25 April 2025
EMA/160870/2025
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Alyftrek

International non-proprietary name: deutivacaftor / tezacaftor / vanzacaftor

Procedure No. EMEA/H/C/006382/0000

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
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# List of abbreviations

| Abbreviation | Term |
|---|---|
| ADME | absorption, distribution, metabolism, and excretion |
| AE | adverse event |
| ALT | alanine transaminase |
| $AR_{AUC}$ | accumulation ratio with respect to AUC |
| AUC | area under the concentration versus time curve |
| $AUC_{0-24h}$ | AUC from the time of dosing to 24 hours |
| $AUC_{0-\infty}$ | AUC from the time of dosing extrapolated to infinity |
| $AUC_{0-tlast}$ | AUC from the time of dosing to the last measurable concentration |
| $AUC_{T}$ | AUC during a dosing interval |
| BA | bioavailability |
| BCRP | breast cancer resistance protein |
| BSEP | bile salt export pump |
| Caco-2 | colorectal adenocarcinoma (cells) |
| $C_{ave}$ | average concentration |
| CF | cystic fibrosis |
| *CFTR* | CF transmembrane conductance regulator gene |
| CFTR | CF transmembrane conductance regulator protein |
| CFU | colony forming units |
| CHMP | Committee for Medicinal Products for Human use |
| CI | confidence interval |
| CL | clearance |
| CL/F | apparent clearance |
| $CL_{ss}/F$ | apparent clearance at steady-state |
| $C_{max}$ | maximum observed concentration |
| $C_{max,ss}$ | maximum observed concentration at steady-state |
| $C_{min}$ | minimum observed concentration |
| CQA | critical quality attribute |
| C-QTc | concentration-QTc |
| CSAP | cardiac statistical analysis plan |
| CSR | clinical study report |
| $C_{trough}$ | predose concentration |
| CV | coefficient of variation |
| CYP | cytochrome P450 |
| DDI | drug-drug interaction |
| D-IVA | deutivacaftor |
| DoE | design of experiments |
| DSC | differential scanning calorimetry |
| DSL | design space limits |
| DVS | dynamic vapour absorption |
| EBE | empirical Bayes estimate |
| EC | effective concentration |
| $EC_{50}$ | concentration at which effect is at half the maximum |
| ECG | electrocardiogram |
| EE | ethinyl oestradiol |
| eGFR | estimated glomerular filtration rate |
| ELX | elexacaftor |
| $E_{max}$ | maximum effect |
| E-R | exposure-response |
| F/F | homozygous for *F508del* |
| F/G | heterozygous for *F508del* and a gating mutation |
| F/MF | heterozygous for *F508del* and a minimal function mutation |
| F/RF | heterozygous for *F508del* and a residual function mutation |
| *F508del* | CFTR gene mutation with an in-frame deletion of a phenylalanine codon |

| Abbreviation | Term |
|---|---|
| | corresponding to position 508 of the wild-type protein |
| FDC | fixed-dose combination |
| FRT | Fischer rat thyroid |
| GC | gas chromatography |
| GLSM | geometric least squares mean |
| HBE | human bronchial epithelial |
| HPLC | high performance liquid chromatography |
| HR | heart rate |
| $IC_{50}$ | concentration resulting in 50% of the maximum inhibition |
| ICH | International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IPC | in-process control |
| IQR | interquartile range |
| IR | Infrared |
| IVA | ivacaftor |
| $K_i$ | inhibition constant |
| $K_m$ | Michaelis-Menten rate constant |
| $\lambda_z$ | terminal phase rate constant |
| LDPE | low density polyethylene |
| LS | least squares |
| MAD | multiple ascending dose |
| MATE | multidrug and toxin extrusion protein |
| max | maximum value |
| MDCK | Madin-Darby canine kidney |
| MEK | methyl ethyl ketone |
| MHI | moderate hepatic impairment |
| min | minimum value |
| MMRM | mixed-effects model for repeated measures |
| MOX | moxifloxacin |
| $MR_{AUC}$ | metabolic ratio for AUC |
| $MR_{AUC\tau}$ | metabolic ration for $AUC_\tau$ |
| $MR_{Cmax}$ | metabolic ratio for $C_{max}$ |
| mRNA | messenger RNA |
| MS | mass spectrometry |
| N | total sample size |
| NA | not applicable |
| NAS | new active substance |
| NMR | nuclear magnetic resonance |
| NOAEL | no-observed-adverse-effect level |
| NOR | normal operating range |
| NR | not reported |
| OATP | organic anion transporter polypeptide |
| OCT | organic cation transporter |
| *P* | probability |
| PBPK | physiologically based pharmacokinetic |
| PBO | placebo |
| PCTFE | polychlorotrifluoroethylene |
| PD | pharmacodynamic, pharmacodynamics |
| PDE | permitted daily exposure |
| P-gp | P-glycoprotein |
| Ph. Eur. | European Pharmacopoeia |
| PIP | paediatric investigation plan |
| PK | pharmacokinetic, pharmacokinetics |
| popPK | population PK |
| $ppFEV_1$ | percent predicted forced expiratory volume in 1 second |
| PR | PR interval, segment |

| Abbreviation | Term |
|---|---|
| PVC | polyvinyl chloride |
| q1w | once weekly |
| q2d | every 2 days |
| q12h | every 12 hours |
| QbD | quality by design |
| QC | quality control |
| qd | once daily |
| Q/F | apparent intercompartmental clearance |
| qod | every other day |
| QRS | the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarisation |
| QT | QT interval |
| QTc | QT interval corrected |
| QTcF | QT interval corrected by Fridericia's formula |
| QTPP | quality target product profile |
| RH | relative humidity |
| SAD | single ascending dose |
| SD | standard deviation |
| SDD | spray dried dispersion |
| SE | standard error |
| SmPC | summary of product characteristics |
| SwCl | sweat chloride |
| $t_{½}$ | terminal phase half-life |
| TAMC | total aerobic microbial count |
| TC | triple combination |
| TCR | triple combination responsive (defined as responsive to ELX/TEZ/IVA) |
| TEZ | tezacaftor |
| TGA | thermo-gravimetric analysis |
| $t_{last}$ | last time point with a concentration above the lower limit of quantitation or the last sampling time in a steady-state dosing interval |
| $t_{max}$ | time of maximum concentration. |
| TRA | total radioactivity |
| TSE | transmissible spongiform encephalopathy |
| TYMC | total combined yeasts/moulds count |
| USP | United States Pharmacopoeia |
| USP/NF | United States Pharmacopoeia/National Formulary |
| UV | ultraviolet |
| V/F | apparent volume of distribution |
| $V_c/F$ | apparent volume of distribution of the central compartment |
| VNZ | vanzacaftor |
| $V_p/F$ | apparent volume of distribution of the peripheral compartment |
| VX-121 | vanzacaftor(VNZ) |
| $V_z/F$ | apparent volume of distribution (based on the terminal phase) |
| XR(P)D | X-ray (powder) diffraction |
| y | years of age |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Vertex Pharmaceuticals (Ireland) Limited submitted on 30 April 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Alyftrek, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 June 2023.

Alyftrek was designated as an orphan medicinal product EU/3/21/2527 on 12 November 2021 in the following condition: treatment of cystic fibrosis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Alyftrek as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/alyftrek

The applicant initially applied for the following indication: *for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one F508del mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see section 5.1, Table 4).*

Alyftrek is a triple combination (TC) regimen composed of three CFTR modulators: two CFTR correctors vanzacaftor (VNZ) and tezacaftor (TEZ), and a CFTR potentiator deutivacaftor (D-IVA), that can be administered in a once daily regimen.

Vanzacaftor works in combination with TEZ and D-IVA to increase CFTR-mediated Cl- transport. VNZ has overlapping binding sites with elexacaftor (ELX, part of Kaftrio), but also has unique binding sites at the CFTR protein. D-IVA is a novel CFTR potentiator and is a deuterated isotopologue of IVA. This modification aims to alter the pharmacokinetic properties (e.g. increase half-life), thereby supporting a once daily dosing regimen (instead of twice daily with IVA). TEZ is also part of previously approved CFTR therapies Symkevi (IVA+TEZ) and Kaftrio (ELX+TEZ+IVA).

## *1.2. Legal basis*

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

This application is a fixed combination medicinal product.

## *1.3. Information on paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0071/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0071/2022 was not yet completed as some measures were deferred.

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

## *1.5. New active substance status*

The applicant requested the active substance deutivacaftor contained in the Alyftrek triple combination medicinal product to be considered as a new active substance on the basis that it is not a constituent of a medicinal product previously authorised within the European Union.

The applicant requested the active substance vanzacaftor contained in the Alyftrek triple combination medicinal product to be considered as a new active substance on the basis that it is not a constituent of a medicinal product previously authorised within the European Union.

Overall the applicant requested Alyftrek medicinal product to be considered as a new active substance on the basis that it is not a constituent of a medicinal product previously authorised within the European Union.

## *1.6. Protocol assistance*

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

| Date | Reference | SAWP co-ordinators |
|---|---|---|
| 25 January 2018 | EMEA/H/SA/3708/1/2017/III | Sheila Killalea, Rune Kjeken |
| 22 February 2018 | EMEA/H/SA/3729/1/2018/I | Sheila Killalea, Rune Kjeken |

The protocol assistance pertained to the following *quality, non-clinical, and clinical*> aspects:

- Quality

Quality by design approach, Active substance specifications and stability data. Quality advice was received by the applicant on the development of deutivacaftor (a deuterated form of ivacaftor) and the acceptability of leveraging the development data from the ivacaftor development to the deutivacaftor dossier.

- Clinical

Clinical bridging study (study design), safety data.

## *1.7. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Mol Co-Rapporteur: Finbarr Leacy

| | |
|---|---|
| The application was received by the EMA on | 30 April 2024 |
| The procedure started on | 23 May 2024 |
| The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on | 12 August 2024 |
| The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on | 26 August 2024 |
| The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on | 26 August 2024 |
| The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on | 19 September 2024 |
| The applicant submitted the responses to the CHMP consolidated list of questions on | 20 December 2024 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on | 03 February 2025 |
| The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on | 13 February 2025 |
| The CHMP agreed on a list of outstanding issues to be sent to the applicant on | 27 February 2025 |
| The applicant submitted the responses to the CHMP list of outstanding issues on | 27 March 2025 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on | 09 April 2025 |
| The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on | N/A |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Alyftrek on | 25 April 2025 |
| Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product on | 25 April 2025 |

# 2. Scientific discussion

## *2.1. Problem statement*

In the current application, the applicant is applyingfor an indication for the new fixed dose combination including 3 different orally administered CFTR modulators i.e. vanzacaftor, tezacaftor and deutivacaftor (VNZ/TEZ/D-IVA) for the treatment of people with cystic fibrosis (CF) aged 6 years and older who have at least one *F508del* or another responsive mutation in the *CFTR* gene.

### 2.1.1. Disease or condition

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 absent or deficient function of the CFTR protein at the cell surface. The most common CFTR mutation is the F508del mutation, which covers about 70-90% of the CF population.

### 2.1.2. Epidemiology

CF affects approximately 54,000 people in Europe (including Russia, Turkey and Israel) and 32,000 in the United States (US). The incidence and prevalence of CF vary between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations.

Overall, a total of > 2000 CFTR mutations have been identified. The most common mutation causing CF is the *F508de*l mutation. About 50% of the CF population is homozygous for the *F508del* mutation, while this allele is present in at least 70% of the overall CF population.

### 2.1.3. Biologic features, aetiology and pathogenesis

The CFTR protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF.

In people with CF, loss of chloride transport due to defects in the CFTR protein result in the 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 people with CF.

The biochemical defect of defective chloride channel function is present from birth, with the sequelae of lung, pancreatic and other organ involvement emerging progressively throughout childhood and into adulthood.

CFTR mutations can be classified according to:

- the mechanism by which the CFTR function is disrupted
    - Class I mutations: Defective protein production
    - Class II mutations: Defective protein processing
    - Class III mutations: Defective regulation
    - Class IV mutations: Defective chloride conduction
    - Class V mutations: Reduced amounts of functional CFTR protein (less transcription)

- the extent of loss of chloride transport caused by the CFTR mutation.
  In general, a complete (Class I) or near complete loss of CFTR chloride transport (class II/III) is referred to as minimal function (MF) of CFTR (class I, II and III). A less complete loss of CFTR-mediated chloride transport is referred to as "residual function" (RF) of CFTR (class IV and V).

### 2.1.4. Clinical presentation, diagnosis

In Europe the median age of all CF patients was 19.8 years (with youngest patient being diagnosed just after birth and the oldest patient being 87.4 years of age) in 2021 according to the 2021 ECFS Patient Registry Annual Data Report. Despite advances in treatment, the current median age of death in a patient with CF is 33 years.

The classic or typical form of cystic fibrosis (CF) is diagnosed if a patient demonstrates clinical disease in one or more organ systems and has elevated sweat chloride (≥60 mmol/L) and harbours 2 CF causing mutations.

SwCl ≥30 to <60 mmol/L represents an indeterminate range, with additional testing needed to support a diagnosis of CF. Within this indeterminate range, CF disease is milder than with SwCl levels >60 mmol/L. SwCl <30 mmol/L is consistent with levels seen in CF carriers (e.g., parents of children with CF), who do not manifest disease and have a normal lifespan.

There is a wide spectrum of severity in CF, even among patients who harbour the same mutations, as modifier genes and environmental factors play also a role in the phenotype. Some patients are severely affected, with symptoms already present at birth (meconium ileus). Most patients develop symptoms during childhood, while some patients may only demonstrate mild or atypical symptoms in adulthood. Usually, patients with Class I-III mutations are more severely affected than those with class IV-V mutations.

SwCl is a predictor of the severity of the disease course of CF. Extensive natural history studies in people with CF across CFTR mutations with varied severity of molecular defects (e.g., reduced or absent protein production; processing, gating, or conduction defects) have demonstrated a relationship between genotype, CFTR function (measured by SwCl) and clinical outcomes as measured by lung function decline, pancreatic function, nutrition and survival.

**Table 1. CFTR function correlation with clinical manifestations of CF disease**

| CFTR Function | SwCl (mmol/L) | Disease Severity | Multi-systemic Disease Manifestations | | | |
|---|---|---|---|---|---|---|
| | | | Lungs | GI | Pancreas | Reproductive |
| Minimal | >80 | Severe | • Early onset of CF lung disease<br>• Rapid lung function decline | • Meconium ileus<br>• Lower BMI | • Pancreatic insufficient<br>• CFRD | • Obstructive azoospermia<br>• Reduced female fertility |
| Residual | ~70 | Attenuated | • Later onset of CF lung disease | • Lower rates of meconium ileus<br>• Higher BMI | • Pancreatic sufficient<br>• Pancreatitis<br>• Lower rate of CFRD | |
| Impaired | ≥30 to <60 | Mildest | • Slowest rate of lung function decline | • Highest BMI | • Pancreatic sufficient | • NR |

**Table 1. CFTR function correlation with clinical manifestations of CF disease**

| CFTR Function | SwCl (mmol/L) | Disease Severity | Multi-systemic Disease Manifestations | | | |
|---|---|---|---|---|---|---|
| | | | Lungs | GI | Pancreas | Reproductive |
| Carrier/ Normal | <30 | None | No CF phenotype, normal survival | | | |

Source: References [3, 4, 6-9, 32, 34-39]

BMI: body mass index; CF: cystic fibrosis; CFRD: cystic fibrosis related diabetes; GI: gastrointestinal; NR: not reported; SwCl: sweat chloride

### 2.1.5. Management

Existing treatments for CF can be broadly classified in two groups: (1) therapies that manage the symptoms, complications, and comorbidities of the disease (e.g., antibiotics, mucolytics, pancreatic enzyme replacement therapy) and (2) CFTR modulators (i.e., correctors and potentiators) that target the underlying cause of the disease. Concomitant administration of these two groups is recommended to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life. However, not all CFTR genotypes are indicated for approved modulator therapies, and not all patients are able to tolerate the therapy.

1) CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences and symptoms of the disease. These therapies are predominantly generic medicines authorised at a national level, apart from agents for the management of chronic pulmonary infections due to *Pseudomonas aeruginosa*.

2) CFTR modulators are small molecules that target specific defects caused by mutations in the CFTR gene. These exist as correctors and potentiators.

   *Correctors* facilitate the cellular processing and trafficking of CFTR to increase the quantity of CFTR protein at the cell surface. Currently approved correctors are lumacaftor, tezacaftor and elexacaftor. *Potentiators* increase the channel open probability (channel gating activity) of the CFTR protein delivered to the cell surface to enhance chloride transport. A currently approved potentiator is ivacaftor (Kalydeco®).

   A combination of a corrector and a potentiator, should result in sufficient levels of CFTR at the surface, which is then enhanced for its gating function. Currently approved combination therapies are lumacaftor/ivacaftor (Orkambi), tezacaftor/ivacaftor (Symkevi) and elexacaftor/tezacaftor/ivacaftor (Kaftrio).

## *2.2. Type of application and aspects on development*

Alyftrek belongs to the pharmacotherapeutic group of other respiratory system products with ATC code R07AX33. Alyftrek is a triple combination product that contains the new CFTR modulator vanzacaftor, and the known CFTR modulator tezacaftor. Deutivacaftor is the deuterated form of the well-known modulator ivacaftor and is not considered a new active substance.

The VNZ/TEZ/D-IVA regimen is composed of 3 CFTR modulators: 2 CFTR correctors (VNZ and TEZ) and a CFTR potentiator (D-IVA) that can be administered as a once daily (qd) regimen.

VNZ and TEZ bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms that can cause defects throughout the CFTR protein (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. D-IVA potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. All 3 binding sites are located away from the site of the defect in F508del-CFTR protein or other VNZ/TEZ/D-IVA-responsive CFTR mutations (as determined in the FRT *in vitro* model) that are important for protein stability and/or function.

The proposed indication for VNZ/TEZ/D-IVA is the treatment of people with CF aged 6 years and older who have at least one F508del or another responsive mutation in the CFTR gene.

The proposed medicinal product is a fixed-dose combination of 3 orally administered small molecules. The dosing regimen is provided in Table 2.

**Table 2. Dosing recommendation for people with CF ≥6 years of age**

| Age | Weight | Dose |
|---|---|---|
| ≥6 years | <40 kg | VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 150 mg qd |
| | ≥40 kg | VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd |

CF: cystic fibrosis; D-IVA: deutivacaftor; qd: once daily; TEZ: tezacaftor; VNZ: vanzacaftor

### *2.2.1 The development programme*

The current clinical development programme for the development of VNZ/TEZ/D-IVA is built on the clinical and regulatory experience obtained in the previous procedures with ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), tezacaftor/ivacaftor (Symkevi) and elexacaftor/tezacaftor/ivacaftor (Kaftrio).

A new variation for Kaftrio/Kalydeco has recently received a positive opinion from the CHMP (EMEA/H/C/005269/WS2551), in Feb 2025 to extend the indication for patients who do not harbour an F508del mutation and who do not have two class I mutations The non-F508del population constitutes about 20% of the overall CF population. This Kaftrio/Kalydeco application was supported with clinical data, *in vitro* data, real world data and literature.

During the procedure, the applicant extended the initially applied indication to seek for the broad indication similar to the extended indication of Kaftrio/Kalydeco, i.e. patients who have at least 1 non-class I mutation in the *CFTR* gene.

A total of 23 mutations (including F508del) have been evaluated in the clinical phase 3 programme. Supportive evidence was obtained by *in vitro* responsiveness to VNZ/TEZ/D-IVA in the Fischer Rat Thyroid (FRT) assay for a total of 522 mutations (including F508del).

For other CFTR mutations, supportive evidence was extrapolated from *in vitro* data and clinical data that were obtained in the previous developments of TEZ/IVA (Symkevi) or ELX/TEZ/IVA (Kaftrio).

**Pivotal trial design**

Up till now, the initial studies to establish the efficacy of the currently approved modulators have been placebo-controlled studies. Placebo-controlled trials might no longer be considered ethical as modulator therapy has become the standard of care in many countries. New treatment can be investigated on top of

another modulator, but additional improvements in lung function, as measured by FEV1, might not be possible due to the ceiling effects of both irreversible lung damage and achieving the maximum physiological lung function.

Therefore, the currently conducted pivotal trials used a non-inferiority design by showing an effect on the FEV1 using ELX/TEZ/IVA (Kaftrio) as comparator. Sweat chloride (SwCl) level was included as key secondary endpoint to show superiority over the active comparator ELX/TEZ/IVA as additional improvement of the SwCl appears to be feasible.

## *2.3. Quality aspects*

### 2.3.1. Introduction

The finished product is presented as film-coated tablets containing 50 mg/20 mg/4 mg or 125 mg/50 mg/10 mg of deutivacaftor, tezacaftor and vanzacaftor (as vanzacaftor calcium dihydrate) respectively as active substances.

Other ingredients are:

Tablet core: croscarmellose sodium (E468), hypromellose (E464), hypromellose acetate succinate, magnesium stearate (E470b), microcrystalline cellulose (E460(i)), sodium laurylsulfate (E487).

Tablet film coat: carmine (E120), brilliant Blue FCF aluminium lake (E133), hydroxypropyl cellulose (E463), hypromellose (E464), iron oxide red (E172), talc (E553b), titanium dioxide (E171).

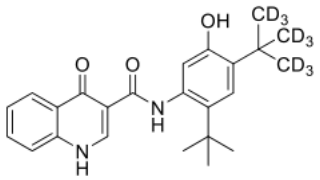
The product is available in thermoform blister consisting of PCTFE (polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a blister foil (aluminium) lidding, as described in section 6.5 of the SmPC.

### 2.3.2. Active Substance: deutivacaftor

#### *2.3.2.1. General information*

The chemical name of deutivacafor (D-IVA) is *N*-(2-(tert-butyl)-5-hydroxy-4-(2-(methyl-d3)propan-2-yl-1,1,1,3,3,3-d6)phenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide corresponding to the molecular formula $C_{24}H_{19}D_9N_2O_3$. It has a molecular weight of 401.55 g/mol and the following structure:

**Figure 1. Deutivacaftor structure**



The chemical structure of deutivacafor was elucidated by a combination of elemental analysis, high-resolution mass spectrum analysis, 1H-NMR and 13C- NMR spectroscopy, infrared (IR), Raman and UV-Visible spectroscopy and crystallographic analysis. The solid-state properties of the active substance were measured by X-Ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and dynamic vapor sorption (DVS).

The active substance deutivacaftor is the deuterated form of ivacaftor (IVA). The active substance is a non-hygroscopic white to off-white solid and is practically insoluble in water and buffers over the physiological pH range.

Deutivacaftor shows polymorphism. Screening of the non-deuterated analogue of deutivacaftor (ivacaftor) identified four polymorphs. Deutivacaftor is manufactured as two forms. The equivalency of the isolated forms of deutivacaftor and ivacaftor was demonstrated.

Since the active substance is completely dissolved in organic solvents at the beginning of the spray-drying process to manufacture the finished product polymorphic form is not a critical quality attribute (CQA) of deutivacaftor active substance and no XRPD control is performed. This is acceptable.

The active substance contains no asymmetric centres. Full information on deutivacaftor has been provided in the dossier.

The development of deutivacaftor was based on the development and commercial experience with ivacaftor active substance. Due to the similarities between deutivacaftor and ivacaftor, significant portions of the ivacaftor development as described in the MAA for Kalydeco were leveraged to the dossier of deutivacaftor. The physical properties of deutivacaftor and ivacaftor were found to be comparable and therefore should not impact the active substance or spray drying process or be detrimental towards stability. The acceptability of use of signification portions of the development of ivacaftor for the deutivacaftor active substance and spray dried dispersion (SDD) is in accordance with previous EMA scientific advice.

The applicant claimed NAS status for deutivacaftor. The CHMP evaluated the justification provided and whereas it is acknowledged that deutivacaftor as such has not been previously authorised in the EU, it is an isotopologue of the authorised ivacaftor where 9 hydrogen atoms have been replaced by 9 deuterium atoms and therefore can be considered a derivative of ivacaftor. Replacement of hydrogen by deuterium (which is a naturally occurring isotope of hydrogen) does not constitute a different elemental structure compared to ivacaftor and thus the therapeutic moiety that patients are exposed to is considered the same. Therefore, the NAS claim for deutivacaftor was not accepted based on its molecular structure (indent 1 of the of Annex I of Chapter 1 of Volume 2A of the Notice to Applicants). A NAS claim under indent 2 may be upheld if it is demonstrated that the change in isotope content leads to significant differences in safety and/or efficacy (see clinical section).

#### *2.3.2.2. Manufacture, characterisation and process controls*

The active substance is manufactured at multiple manufacturing sites. Satisfactory GMP documentation has been provided.

The synthesis of deutivacaftor comprises three chemical transformation steps with one isolated intermediate from the starting material.

To note, in the original submission the applicant proposed an alternative starting material. This was not considered acceptable by CHMP as this compound is introduced relatively late in the synthesis with no

isolated intermediates afterwards. The CHMP requested to redefine the starting material to the same starting material used for that branch in the synthesis of the approved ivacaftor (major objection, MO1) and redefinition was performed.

Organic solvents used in the last step of the synthesis are ICH class 2 solvents. No class 1 organic solvents are used. Palladium is used as metal catalyst in the first step of the synthesis and controlled in an intermediate specification.

The manufacturing process has been described in sufficient detail. The manufacturing process description and level of detail is comparable to that of ivacaftor.

The choice of the starting materials is acceptable. The starting materials are basically the same as have been approved for ivacaftor (IVA). Names and addresses of the starting materials suppliers have been laid down and sufficient information on the synthesis of the starting materials has been provided.

The control strategy for potential impurities from the starting material synthesis was based on the experience and spike and purge studies performed with IVA and were leveraged to D-IVA. This is acceptable as the behaviour of D-IVA in the synthesis is expected to be the same as for IVA. During the review, the applicant confirmed that the control of the desired deuterated regioisomer is assured by the chemistry used to introduce the deuterated t-butyl group.

The specification for one of the starting materials is the same as approved for IVA. The specification for the other starting material is identical to that of the non-deuterated form of the same starting material as authorised for the synthesis of IVA, except for an additional isotopic purity test in its specification. The specifications are acceptable.

The reagents and solvents used in the synthesis of D-IVA and control thereof are the same as those in IVA. This is acceptable.

The control of critical steps, in-process controls (IPCs) and intermediates has been sufficiently described and are in line with the synthesis of IVA. The specifications for the intermediates are the same as that for the IVA intermediates.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes made from the 2nd generation process to the commercial process did not impact on the active substance impurity profile and final quality. Overall, changes introduced have been presented in sufficient detail and have been justified.

Comparability between D-IVA and IVA has been confirmed by the physical and chemical comparison. As the route of synthesis of D-IVA is the same as that of IVA, it is justified to leverage the experience gained with IVA to the D-IVA dossier, including the control strategy for impurities.

The design spaces from IVA were adopted for D-IVA and were shown to be suitable for D-IVA by performing confirmatory runs at the edges of the design space using D-IVA starting materials and intermediates. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

All active substance CQAs that are potentially impacted by the process parameters of the manufacturing process are routinely controlled.

The active substance is packaged in double LDPE bags that are placed in a container suitable for storage and shipping. The LDPE resin used to manufacture the bags complies with Regulation 10/2011 as amended and Ph.Eur.3.1.3 (polyolefins). The specification for the control of the primary LDPE bags is acceptable.

#### *2.3.2.3. Specification*

The active substance specification includes tests for appearance (visual), identification (IR, Ph. Eur.), assay (HPLC), organic impurities (HPLC), residue on ignition/sulphated ash (Ph. Eur.) and residual solvents (GC).

The active substance specification is based on the active substance CQAs. The CQA identified are appearance, identification, assay, organic impurities, inorganic impurities, palladium, isotopic purity and residual solvents. The omission of a test for isotopic purity from the active substance specification is justified. The deuteration of the D-IVA active substance is incorporated into the structure through the manufacture of the starting material and isotopic purity is maintained throughout manufacture and on stability of D-IVA (both confirmed by supportive data). Control of isotopic purity in the starting material is therefore considered sufficient. Justifications for not including tests for acetamide (hydrolysis by-product of acetonitrile), benzene, particle size, physical form, palladium, water content and microbiological testing were also provided and considered acceptable.

Overall, the active substance specification is acceptable. The specification is in line with the specification of IVA.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. The methods are the same as used for IVA. The stability indicating nature of the HPLC method for assay and organic impurities was confirmed by forced degradation studies using IVA as surrogate for D-IVA (see stability section below). This is acceptable.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for 13 D-IVA pilot and commercial scale batches used for non-clinical, clinical and formal stability studies and those intended for future clinical or commercial use have been provided, demonstrating compliance with the active substance specifications.

#### *2.3.2.4. Stability*

Stability data from three pilot and three commercial scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions (25ºC / 60% RH), for up to 36 months under intermediate conditions (30ºC / 65% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, assay, organic impurities, isotopic purity, water content (KF), microbial limits, water activity. The analytical methods used were the same as for release and were stability indicating.

No clear changes or trends were observed in any of the tested parameters at all three storage conditions. All results were in compliance with the active substance specification.

Photostability testing following the ICH guideline Q1B was performed on IVA as surrogate for D-IVA. This is acceptable since, as indicated earlier, D-IVA and IVA physical and chemical properties were found to be comparable. In addition, the deuterated t-butyl functionality plays no role in potential degradation pathways, as the primary functionality involved in degradation is the amide bond, which is identical between deutivacaftor and ivacaftor. Therefore, any degradation would be the same between both molecules. No differences in appearance, water content, assay, organic impurities and physical form were observed in the ICH Q1B exposed sample compared to a dark control sample. Therefore, deutivacaftor does not require light protection.

Ivacaftor was also used as a surrogate for deutivacaftor in forced degradation studies. Ivacaftor active substance was subjected to stress conditions, which included heat, heat/humidity, treatment under acidic, basic, and oxidative conditions, and exposure to ultraviolet (UV) and light. The results confirm that commercial HPLC methods for ivacaftor active substance assay and organic impurities determination are stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months without any special storage conditions in the proposed container.

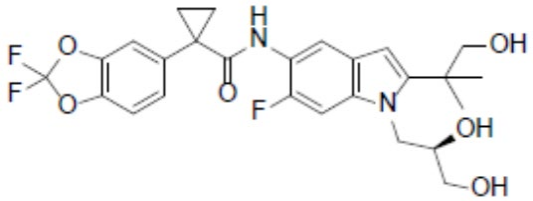
## 2.3.3. Active Substance: tezacaftor

The information for the active substance tezacaftor was not assessed as part of this marketing authorisation application (MAA) since the quality information regarding tezacaftor active substance was previously assessed and approved as part of the Symkevi and Kaftrio marketing applications (EMEA/H/C/004682 and EMEA/H/C/005269 respectively) and an identical Module 3 content has been submitted with this MAA.

### *2.3.3.1. General information*

The chemical name of tezacaftor is: 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide corresponding to the molecular formula $C_{26}H_{27}N_2F_3O_6$. It has a molecular weight of 520.50 g/mol and the following molecular structure:

**Figure 2. Tezacaftor structure**



Tezacaftor exhibits stereoisomerism due to the presence of one chiral centre. The active substance is the R-isomer. The chirality of the active substance is assured by chiral control of the starting materials. The downstream chemistry does not promote racemisation of the stereocentre. This was supported by spiking and stability studies.

The chemical structure of tezacaftor was elucidated by a combination of elemental analysis, $^{1}H$, $^{13}C$, and two-dimensional NMR spectroscopy, UV/Vis, IR and Raman spectroscopy, high resolution mass spectrometry and crystallographic analysis.

Tezacaftor is a non-hygroscopic white to off-white crystalline solid. The substance is practically insoluble in aqueous solvents and more soluble in organic solvents. Because of its poor solubility in water, a SDD, where the active substance is in an amorphous form to provide sufficient oral bioavailability was developed (see finished product section).

Physical characterisation of tezacaftor was conducted by X-ray powder diffraction, differential scanning calorimetry, thermal gravimetric analysis and dynamic vapour sorption. The physical form of tezacaftor active substance manufactured by the proposed commercial process is the most thermodynamically stable crystalline neat form. To understand the polymorph landscape of tezacaftor, a comprehensive polymorph screening for neat forms, solvates, and hydrates was conducted. Two neat forms were found. No hydrate has been found from multiple aqueous-based solvent systems.

During the manufacture of the SDD, tezacaftor is completely dissolved in a process solvent, therefore polymorphic form and particle size are not CQAs.

#### *2.3.3.2. Manufacture, characterisation and process controls*

The active substance is manufactured at multiple manufacturing sites. Satisfactory GMP documentation has been provided.

The commercial manufacturing process for the synthesis of tezacaftor involves seven steps from commercially available well-defined starting materials with acceptable specifications and several crystallisations.

The selected starting materials in the synthesis are approvable, in view of ICH Q11 and its Q&A, and the CHMP guideline on chemistry of the active substance (EMA/454576/2016); sufficient justification and discussion for the choice of these compounds is provided. The names and addresses of the starting material manufacturers/suppliers are laid down in the dossier. This also holds regarding the synthesis routes of the starting materials applied by the manufacturers/suppliers. Two active substances manufacturers which use the same route of synthesis are proposed.

Following an enhanced QbD quality approach, the tezacaftor active substance manufacturing process was risk assessed to determine which process parameters had the potential to have the greatest impact on tezacaftor CQAs. On this basis, both critical and non-critical parameters have been defined to describe the manufacturing process and process controls. Design spaces have been established for several process steps, based on Designs of experiments (DOE) studies performed.

Design space verification was completed for each unit operation in line with EMA "Questions and Answers on Design Space Verification" (EMA/603905/2013). This design space verification and lifecycle management were based on a risk assessment of potential scale dependent phenomena for each step along with the control strategy demonstrated during development studies. As a result, none of the design spaces were

categorised as high risk but as medium scale-up risk. Thus, well-established chemical engineering science and scale-up principles (e.g. heat transfer, solids suspension, liquid blending) and correlations were used to examine potentially scale-dependent phenomena and confirm that they do not impact process performance, and that the design spaces developed at laboratory scale apply to (are verified for) commercial scale. The consistency of commercial scale batches with lab scale predictions provided further support for the design space scale verification conclusions.

Adequate IPCs are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The tezacaftor active substance control strategy comprises the starting materials, reagents and solvents specifications, the active substance synthesis design spaces, IPCs and active substance specification. The impurity data and justifications (including purge and fate studies) support the control strategy; absence of carry-over of impurities through the synthesis has sufficiently been demonstrated and the control strategy is in line with the guidelines (e.g. ICH Q3A, Q3C, M7, Q11).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Detailed information regarding the manufacturing process development of tezacaftor active substance has been presented. The changes made during development are considered minor and are not expected to impact on the quality of the active substance.

The active substance is packaged inside a LPDE bag and secured with an appropriate closure (twist tie or equivalent). The bag is then placed inside a second LDPE bag and secured appropriately; the closed LDPE bags are placed into a secondary container suitable for storage and shipping which complies with the European Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03). The LDPE resin used to manufacture the bags is suitable to be in contact with food and complies with the requirements of Commission Regulation (EU) No 10/2011 and the Ph.Eur. Monograph 3.1.3 "Polyolefins".

#### *2.3.3.3. Specification*

Tezacaftor specification includes tests and limits for appearance (visual), identification (IR), assay (HPLC), organic impurities (HPLC), inorganic impurities: palladium (Ph. Eur.) and residue on ignition/ sulphated ash (Ph. Eur.) and, residual solvents (GC).

The active substance specification is based on the active substance CQAs. The CQA identified are appearance, identification, assay, organic impurities, chiral purity, inorganic impurities, residual solvents, palladium and copper. A justification for the absence of control of chiral purity, copper, heavy metals, residual trimethylamine, water content, physical form, particle size and microbial count has been provided and is considered acceptable.

Specifically, the absence for a control of chiral purity has been justified on the basis that tezacaftor contains a single chiral centre, which is a secondary carbinol. The tezacaftor enantiomer, arises from an enantiomeric impurity in one of the starting materials. The downstream chemistry does not promote racemisation of the stereocentre, and no racemisation was observed during tezacaftor active substance stability studies. In order to accomplish racemisation, a multi-step procedure with specific conditions would be required. Therefore, the control of chiral purity of tezacaftor active substance is established according to ICH Q6A (decision tree #5) by applying limits in the starting material as supported by development studies. The carry over studies and

design spaces studies showed that the stereo-chemical enantiomers, if formed, do not carry through the synthesis and that the limit established at starting material level is adequate. This justification is acceptable.

Elemental impurities are controlled in line with ICH Q3D.

All solvents are control well below the option 1 limit in draft ICH Q3C (R6).

Water content is not a CQA of tezacaftor because the crystalline active substance is non-hygroscopic and water does not affect active substance stability or finished product manufacture.

With regards to active substance polymorphism, physical form has been monitored during all development and stability studies. To date, there has been no change in the tezacaftor polymorphic form. In addition, the active substance fully dissolves in organic solvents at the beginning of the spray-drying process. Form A is freely soluble at the maximum solids load in the spray drying solvent system. For this reason, polymorphic form is not a CQA of the tezacaftor active substance and it is not included in its specification.

Likewise, particle size of tezacaftor is not a CQA because the active substance is completely dissolved in the spray drying solvent system as the first step of the SDD manufacture.

Tezacaftor has not been shown to be bactericidal or bacteriostatic. However, the active substance manufacturing process follows classic chemical synthesis which is hostile to microorganisms. In addition, the microbial limits and water activity test results from 3 representative active substance lots presented show very low bioburden, absence of specified microorganisms using validated compendial microbial limits methods, and water activities less than 0.6 (consistent with the fact that the active substance has low hygroscopicity and indicating the material is not likely to support microbial growth).

The primary stability data showed that water activity levels remain below the threshold for microbial growth promotion (0.6), and no change in microbial content after storage for 12 months at 25°C/60% RH in the intended container closure system. These combined data indicate that tezacaftor active substance possesses very low risk of microbial contamination and microbial testing of commercial batches is not necessary.

The tests and limits in the specifications are considered appropriate for controlling the quality of this active substance.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

All batch results (including those of the batches used in the clinical studies) are in compliance with the proposed specification.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay and impurities testing has been presented.

Batch analysis data on several pilot or commercial scale batches of the active substance used for non-clinical studies, clinical studies, and formal stability studies, or intended for future clinical or commercial use were provided. All results are within the proposed specifications and consistent from batch to batch.

#### *2.3.3.4. Stability*

Stability data on three primary stability batches and three commercial batches stored in the intended commercial package for up to 60 months under long term conditions (25°C/60% RH) and for up to 6 months under accelerated conditions (40°C/75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, organic impurities, chiral purity (HPLC), water content (KF titration), physical form (XRPD), microbial limits (USP <61> and <62>), specified microorganisms (E. coli) and water activity (USP <1112>). All results under long term and accelerated stability conditions met the acceptance criteria for the attributes evaluated and no trends were observed. Water activity levels remained below the threshold for microbial growth promotion (0.6), and no change in microbial content after storage for 60 months at 25°C/60% RH in the intended container closure system was observed. The stability data show that tezacaftor active substance is stable when packaged in the intended container closure system under all storage conditions.

Photostability testing following the ICH guideline Q1B option 2 was performed on one batch. Samples were tested for appearance, assay, organic impurities and chiral purity. The data, showing no changes in the fully exposed test sample and the covered control, confirm that tezacaftor active substance is photostable and does not require light protective packaging.

Results from stress studies including heat (80°C), heat/humidity (80°C/75%RH), treatment under acidic (0.2N HCl, ambient), basic (0.2N NaOH, ambient), and oxidative (0.02% $H_2O_2$, ambient) conditions for up to 14 days, and exposure to UV and visible light (solid and solution) were also provide on one batch. Tezacaftor was found to be the least stable under the oxidative condition and when exposed to light stress conditions in solution. Results from the primary stability studies demonstrate that none of the degradation products observed under these stress conditions are found at or above the reporting threshold when the active substance is packaged and stored according to label requirements. No degradation was observed when tezacaftor was exposed to the other stress conditions listed above.

All tezacaftor samples from this study were tested for spectral peak purity. The tezacaftor peak was found to be spectrally pure in all stressed samples demonstrating that the commercial HPLC method for assay and organic impurities determination of tezacaftor active substance is stability indicating.

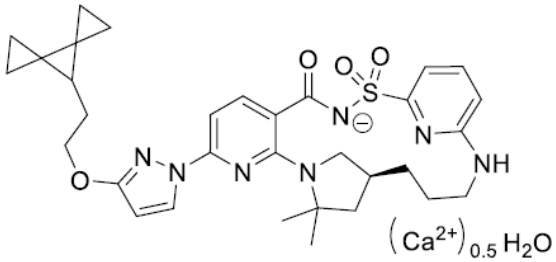
The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored in the proposed container at no more than 30°C.

## 2.3.4. Active Substance: vanzacaftor

#### *2.3.4.1. General information*

The chemical name of vanzacaftor is calcium bis((14S)-8-[3-(2-{dispiro[2.0.2⁴.1³]heptan-7-l}ethoxy)pyrazol-1-yl]-12,12-dimethyl-2,2,4-trioxo-2λ⁶-thia-3,9,11,18,23-pentaazatetracyclo[17.3.1.1¹¹,¹⁴.0⁵,¹⁰]tetracosa-1(23),5,7,9,19,21-hexaen-3-ide) corresponding to the molecular formula $C_{32}H_{38}N_7O_4S•Ca_{0.5}•H_2O$. It has a relative molecular mass of 654.82 g/mol and the following structure:

**Figure 3. Vanzacaftor structure**




The chemical structure of vanzacaftor was elucidated by a combination of elemental analysis (C, H, N, Ca), high-resolution mass spectrum analysis, NMR spectroscopy (1H, 13C, 1H-1H gCOSY, megHSQC, gHMBC), infrared (IR), Raman and UV-Visible spectroscopy and crystallographic analysis. The solid state properties of the active substance were measured by XRPD, DSC, TGA and DVS. The structure has been sufficiently elucidated, including the stereochemistry (S configuration) and polymorphic form (vanzacaftor calcium salt Form D).

The active substance is a white to off-white slightly hygroscopic crystalline variable hydrate solid and is practically insoluble in water and buffers over the physiological pH range. Full information on vanzacaftor has been provided in the dossier.

The active substance contains one chiral centre in the S configuration. The vanzacaftor enantiomer arises from an enantiomeric impurity in one of the starting materials. The downstream chemistry does not allow for racemisation of the stereocentre during the manufacture of vanzacaftor active substance. An increase in the level of the enantiomeric impurity has not been observed throughout development. Therefore, the control of the enantiomeric impurity of vanzacaftor active substance is established according to ICH Q6A (decision tree #5) by applying limits to the enantiomeric impurity in the starting material.

Vanzacaftor shows polymorphism and is manufactured as vanzacaftor calcium salt dihydrate. Polymorph screening over the course of development identified several metastable hydrated forms of vanzacaftor calcium salt. There are only two hydrated forms relevant to the manufacturing process of vanzacaftor calcium salt, whose interconversion to the desired form is controlled during the last step of the synthesis. In addition, several solvated forms were observed for vanzacaftor calcium; however, none are relevant to the vanzacaftor active substance isolation process.

Stereochemistry and polymorphic form have been shown stable upon storage.

### *2.3.4.2. Manufacture, characterisation and process controls*

The active substance is manufactured at one manufacturing site. Satisfactory GMP documentation has been provided.

Vanzacaftor is synthesised in 4 main steps using well defined starting materials with acceptable specifications.

To note, in the original submission the applicant proposed a different starting material. This was not considered justified given the limited number of chemical transformation steps after its introduction, and

CHMP requested the redefinition to an earlier stage of the synthesis (MO2). Redefinition of the starting material was performed and justified. Based on the provided information and in line with ICH Q11, the redefined starting material was accepted.

A schematic representation of the manufacturing process and a sequential procedural narrative have been provided. The manufacturing process has been described in sufficient detail.

No critical steps in the manufacture have been identified. Adequate in-process controls are applied during the synthesis.

The choice of the starting materials is acceptable. Names and addresses of the starting materials suppliers have been laid down and sufficient information on the synthesis of the starting materials has been provided. The test and proposed limit for enantiomeric impurity as included in the starting material specification are considered adequate to control the correct stereochemistry of the vanzacaftor active substance.

The specifications and control methods for intermediate products, starting materials, and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. No genotoxic impurities were identified by the applicant (see non-clinical section);

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme.  An adequate overview of all changes applied to the manufacturing process from the original process onwards, has been presented. Changes introduced have been presented in sufficient detail and have been justified.

Design spaces were established for some steps of the synthesis. For the study of the process parameters of the steps of the manufacturing process which were assessed as having a medium or high potential to impact CQAs, a DOE was used. No process parameters were identified as being critical and active substance CQAs that are potentially impacted by the studied process parameters are routinely controlled. So, overall, the results of this DOE together with the further control strategy is considered sufficient to support the proposed design spaces.

All vanzacaftor drug substance design spaces were developed at laboratory scale and are expressed in terms of scale-independent parameters, such as temperature, reactant or reagent equivalents and solvent volumes. However, the validity of vanzacaftor design spaces at manufacturing scale could be impacted by factors such as the ability to adequately suspend solids, control temperature for exothermic reactions, or control particle breakage phenomena associated with the wet milling operation, among other phenomena. To assess these scalability risks, engineering calculations were used for various unit operations to ensure that the design spaces developed at the lab scale are applicable and verified for the commercial scale process. The consistency of the commercial-scale batches with lab-scale predictions provided further support and evidence for the design space scale verification conclusions discussed. Overall, the available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

The active substance is packaged in low-density polyethylene (LDPE) bag and secured with an appropriate closure (twist tie or equivalent). The LDPE bag is then placed inside a second LDPE bag and secured appropriately; the closed LDPE bags are placed into a foil bag. The sealed foil bag is placed in a container suitable for storage and shipping. The container closure system for vanzacaftor drug substance was

developed in accordance with the European Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03). The LDPE resin used to manufacture the bags is suitable to be in contact with food and complies with the requirements of Commission Regulation (EU) No 10/2011, as well as Ph. Eur. 3.1.3 "Polyolefins".

#### *2.3.4.3. Specification*

The active substance specification includes tests for appearance (visual), identification (IR, Ph. Eur.), assay (HPLC), organic impurities (HPLC), residual solvents (GC), physical form (XRPD, Ph.Eur.), inorganic impurities (Ph. Eur.), calcium content (IC), water content (KF, Ph. Eur.), and particle size (laser diffraction).

The active substance specification is based on the active substance CQAs. The CQA identified are appearance, identification, physical form, assay, organic impurities, enantiomeric impurity, inorganic impurities (Li, Pd), calcium content, residual solvents, particle size and microbial attributes.

The set parameters and specified limits are acceptable for the control of the active substance. The proposed specification limits for two specified impurities exceed the qualification threshold. This is acceptable as these limits have been toxicologically qualified and are supported by the available batch release and stability data for batches representative of the commercial process. Omission of a test and limit for enantiomeric impurity in the active substance specification has been sufficiently justified as correct stereochemistry is adequately controlled by a test and limit (i.e. NMT 0.50%) for enantiomeric impurity in the starting material specification as discussed above. A justification for the absence of control of benzene, residue on ignition/sulphated ash and microbiological testing was also presented and accepted.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The presented batch analysis results for several pilot and commercial scale batches used in the clinical and/or formal stability studies comply with the active substance specification and confirm batch-to-batch consistency for the batches manufactured according to the commercial process.

#### *2.3.4.4. Stability*

Stability data from three commercial scale batches of active substance from the <proposed> manufacturer stored in the intended commercial package for up to 12 months under long term (25 ºC / 60% RH) and intermediate (30°C/65% RH) conditions and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, organic impurities, enantiomeric impurity, water content, physical form, microbial limits (TAMC, TCYMC, E.coli), water activity and particle size distribution. The analytical methods used were the same as for release and were stability indicating

All results were found well within the specification acceptance limits, and no trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one commercial scale batch. Samples were tested for appearance, water content, assay and organic impurities. Changes in assay and organic impurities were observed in the light exposed sample as compared to the covered control, indicating that vanzacaftor active substance requires light protective packaging for long-term storage. Therefore, the intended container closure system includes a foil bag to provide protection from light.

Results on stress conditions including thermal, thermal/humidity, treatment under acidic, basic, and oxidative conditions, and exposure to ultraviolet (UV) and visible light were also provided one commercial scale batch. The results demonstrated that HPLC methods for vanzacaftor active substance assay and organic impurities determination are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored in the proposed container closure system in order to protect from light.

## 2.3.5. Finished Medicinal Product

### *2.3.5.1. Description of the product and pharmaceutical development*

The finished product is an immediate-release film-coated tablet for oral administration. The product is a fixed dose combination (FDC) of the active ingredients deutivacaftor (D-IVA, VX-561), tezacaftor (TEZ, VX-661) and vanzacaftor calcium dihydrate (VNZ, VX-121).

The product is available in two strengths:

- 50 mg/20 mg/4 mg: Purple film-coated tablet, debossed with "V4" on one face and plain on the other face. The tablet is round-shaped with a diameter of approximately 7.35 mm.
- 125 mg/50 mg/10 mg: Purple film-coated tablet, debossed with "V10" on one face and plain on the other face. The tablet is capsule shaped with dimensions of approximately 15 x 7 mm.

The active substances, vanzacaftor, tezacaftor, and deutivacaftor, are incorporated into the tablets as a crystalline drug substance and two amorphous spray dried dispersions (SDDs), respectively.

Sufficient information on the finished product appearance and composition has been provided. The D-IVA SDD composition, including excipients and processing solvents, is the same as IVA-SDD.

The different tablet strengths are qualitatively the same and are quantitatively proportional with regard to their tablet cores. The applied Opadry film-coating used for the different strengths has a slightly different quantitative composition.

The different tablet strengths are sufficiently visually distinguishable by their colour, size, shape and debossing. The film-coat of the 50 mg/20 mg/4 mg tablets has a lighter colour, due to lower amounts of colourants.

The products are indicated for use in paediatric patients aged 6 years and older. The tablets should not be chewed, crushed, or broken before swallowing because there are no clinical data currently available to support other methods of administration. There are no direct safety issues foreseen with the excipients and their quantities for use in children aged 6 years and older. The lower strength tablets are relatively small, with a diameter of 7.35 mm, so no major swallowability issues are expected. In comparison, the lowest strength of the Symkevi film-coated tablets also authorised for children aged 6 years and older have a size of 12.70 x 6.78 mm and are also to be swallowed whole for the same reason. The excipients used in Alyftrek tablets have all been previously used in formulations for paediatric populations 6–11 years of age, such as the Kaftrio or Orkambi tablets. Overall, the proposed product can be considered age appropriate. In addition, it is noted that the development of an age-appropriate oral formulation for children from 1 year to less than 6

years of age is part of the agreed measures in PIP decision number P/0071/2022 (EMEA-C1-003052-PIP01-21).

The finished product and manufacturing process development were conducted using a QbD approach. A quality target product profile (QTPP) was defined, potential CQAs were identified, an initial risk assessment performed, criticality determined, design space and control strategy established and a final risk assessment performed. Continued process verification and improvement are implemented according to ICH Q10.

The QTPP for Alyftrek was to develop safe and efficacious, bioavailable, immediate release fixed-dose combination tablet of deutivacaftor/tezacaftor/vanzacaftor50 mg/20 mg/4 mg or 125 mg/50 mg/10 mg for oral administration with at least 24-month shelf-life at room temperature packaged in blister.

The CQAs identified were appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, physical form, residual solvents, microbial limits, elemental impurities, enantiomeric impurities and isotopic purity.

The formulation and manufacturing development have been evaluated through the use of risk assessments and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

Both deutivacaftor and tezacaftor are practically insoluble in their crystalline forms. To improve aqueous solubility of these active substances, deutivacaftor and tezacaftor are incorporated in the finished product as individual spray-dried dispersions (SDD). In the SDDs D-IVA and tezacaftor are in the amorphous form. Absence of crystalline tezacaftor and deutivacaftor is controlled as part of the TEZ SDD and D-IVA SDD specifications The choice to incorporate deutivacaftor and tezacaftor in the finished product as SDDs was based on development studies and experience from the applicant with the authorised products containing ivacaftor and tezacaftor (Kalydeco, Symkevi, Kaftrio). As indicated under the active substance section, vanzacaftor is supplied as Form D vanzacaftor calcium dihydrate, which is controlled as part of the active substance specification. Based on further studies on the solid state of the active substances during manufacture and storage of the finished product, it was sufficiently demonstrated that such changes are highly unlikely under normal conditions of storage. No further control of the solid state is therefore needed in the finished product.

There are no concerns regarding the stereochemistry of the three active substances during manufacture and storage of the finished product. Deutivacaftor contains no asymmetric centre in its structure. Tezacaftor and vanzacaftor both contain one chiral centre and are manufactured as pure enantiomers. The absence of the enantiomer impurities of these active substances has been demonstrated as part of the finished product stability studies, confirming that no racemisation occurs during manufacture and storage of the finished product. No additional control is needed.

The choice of the excipients and their functions is briefly described. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. monographs where available or with in-house specifications (MEK and film-coating mixtures). An adequate discussion on the omission of control of functionality-related characteristics of the excipients has been provided. The excipients specifications are acceptable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The compatibility of the active substances with the excipients was confirmed in a stability study with the 125 mg/50 mg/10 mg tablets, that showed the stability of the product after three months storage at 40°C/75% RH in an open dish.

A summary of the formulations used throughout the clinical development has been provided, including an oral suspension, a solution and various tablet dose strengths.

Initial deutivacaftor, tezacaftor and vanzacaftor combination therapy studies were conducted with individual tablets containing one of the active substances. To enhance patient compliance, a fixed-dose combination (FDC) tablet formulation that included all three active components was developed that was used in the Phase 3 studies. Vanzacaftor calcium salt form D dihydrate was used in the Phase 3 studies.

The composition of the quantitatively proportional tablets of 50 mg/20 mg/4 mg and 125 mg/50 mg/10 mg as used in the phase 3 studies has been provided. The compositions are the same as that of the commercial formulations as given in section 3.2.P.1, and therefore are considered representative for the proposed commercial formulation.

The dissolution method development has been adequately described and the choices made were justified. The development was performed separately for the three active substances, resulting in the use of the same dissolution method for vanzacaftor and deutivacaftor and a different quality control dissolution method for tezacaftor. The discriminatory power of the finalised dissolution methods has been adequately demonstrated for these methods and for all three active substances by making deliberate changes in relevant material attributes, tablet composition and process parameters.

QbD experiments for blending (intragranular, extragranular, and lubrication), dry granulation (roller compaction) and milling, tablet compression and film coating were performed to evaluate the potential impact of material attributes and process parameters identified in the initial risk assessments on finished product CQAs. The choice of material attributes and parameters for multivariate experimentation was based on risk assessment and desired operational flexibility.

The performed DOE studies and overall control strategy are sufficient to support the design spaces that have been proposed for the manufacturing process. The representativeness of the manufacturing process development DOE studies for the final manufacturing process and scale has been discussed and justified where relevant.

The primary packaging is thermoform blister consisting of PCTFE (polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a blister foil (aluminium) lidding. All packaging components comply with EU Regulation 10/2011. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

#### *2.3.5.2. Manufacture of the product and process controls*

The finished product is manufactured at one manufacturing site. Satisfactory GMP documentation has been provided.

The manufacturing process consists of a batch manufacturing process comprising six steps: intragranular blending, dry granulation and milling, extragranular blending, extragranular lubrication, compression, and film coating.

The manufacture of the tezacaftor SDD is a multi-step process comprising solution preparation, spray drying, and secondary drying.

The deutivacaftor SDD development was based on the development and commercial experience with ivacaftor SDD. D-IVA and IVA SDD have the same composition and are manufactured using the same process and equipment train. The manufacturing of D-IVA SDD comprises solution preparation, spray drying and secondary drying. The design space proposed for the manufacture of D-IVA SDD is comparable to that for the authorised IVA SDD and is acceptable

The manufacturing process has been described in sufficient detail. Critical as well as non-critical process parameters have been sufficiently laid down for both strengths in the manufacturing process description.

A post approval change management protocol (PACMP) on the management of post approval changes to the current design space for the tezacaftor SDD spray drying manufacturing process has been provided. Although the proposed PACMP seems relatively broad and does not describe specific changes to specific process parameters within the design space. The proposals for the experimental plan, the acceptance criteria and regulatory reporting category and filing requirements are acceptable.

Bulk tablets are packaged into two LDPE bags then placed into a laminated foil bag and heat sealed. The bulk hold time is 24 months when stored at ≤ 30°C in the bulk pack (see stability section).

The provided information on the critical steps and critical process parameters is in line with the development data.

Based on the development DOE studies compression force was identified as CPP for both tablet strengths for the finished product CQAs of dissolution and appearance. Acceptance criteria for the control of tablet hardness as in-process control have therefore been tightened based on the development study results. Furthermore, appearance is evaluated as IPC during the manufacturing process and dissolution is routinely tested as part of the finished product release specification.

For the 50 mg/20 mg/4 mg tablets in addition to compression force also roll force and turret speed (converted to dwell time) were identified as CPPs with a potential effect on uniformity of dosage units for all three active substances. Uniformity of dosage units is routinely controlled as part of the finished product specification.

Design spaces have been proposed for the following steps of the manufacturing process of the medicinal product: intragranular blending, extragranular lubrication and granulation and compression steps.

The representativeness of the manufacturing process development DOE studies for the final commercial manufacturing process and scale has been discussed and justified where relevant. The currently proposed manufacturing process and process parameter settings are sufficiently supported by the available manufacturing process development data, the proposed control strategy and batch analysis data.

The IPCs are adequate for this type of manufacturing process. Satisfactory blend uniformity of the intragranular and extragranular blend were achieved for all runs in the multivariate DOE studies where the blending process was evaluated. This is sufficient to justify the omission of blend uniformity testing as IPC.

The manufacturing process can be considered a standard process for the applicant given his experience with this process. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Therefore, it is accepted that the process validation of the FDC tablets will be performed post-approval in line with the process validation schemes provided for both finished product strengths in section 3.2.R of the dossier. These validation schemes do not cover the manufacture of the tezacaftor SDD. This is acceptable since this finished product intermediate is the same as already authorised

for Symkevi and Kaftrio from the same applicant. The deutivacaftor SDD process was adequately validated on three full scaled batches at the commercial manufacturing site in line with a process validation scheme provided in 3.2.R. An on-going (continued) process verification approach is planned.

#### *2.3.5.3. Product specification*

The finished product release specifications include appropriate tests for this kind of dosage form appearance (visual), identification (IR), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (HPLC), water content (KF) and microbial limits (Ph. Eur.).

The finished product specification is acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Using the Option 1 and Option 2 b approaches it has been demonstrated that all Class 1 and Class 2A elemental impurities in the drug products will be consistently below 30% of the PDEs. This was further confirmed by batch data (Cd, Pb, As, Hg, Co, V and Ni) on three representative pilot scale clinical batches of 50 mg/20 mg/4 mg tablets and four representative pilot scale clinical batches of 125 mg/50 mg/10 mg tablets.

The elemental impurities intentionally added in the vanzacaftor, tezacaftor, and deutivacaftor active substances manufacturing processes are controlled in the respective active substances to levels that ensure the VNZ/TEZ/D-IVA tablets conform to ICH Q3D (R2) requirements.

Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Following a request from CHMP (MO3), a risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Manufacturing steps of the active substances (and their starting materials), SDDs and finished product were evaluated for the use of secondary or tertiary amines and nitrosating agents in the same step. Storage and packaging, use of recovered solvents, excipients and cross-contamination were also considered. The omission of confirmatory testing for the theoretical active substance related nitrosamine impurities N-nitroso-vanzacaftor and N-nitroso-deutivacaftor has been adequately justified by demonstrating the inability to synthesise these compounds under exaggerated nitrosating conditions. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The stability indicating nature of the HPLC methods for assay and degradation products has been demonstrated by means of forced degradation studies. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three pilot scale batches of 50 mg/20 mg/4 mg tablets and five pilot scale batches of 125 mg/50 mg/10 mg tablets confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

### *2.3.5.4. Stability of the product*

Stability data from three pilot scale batches of each strength of finished product stored for up to 18 months under long term (25ºC / 60% RH) and intermediate term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of Alyftrek are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, enantiomeric impurities, dissolution, water content, physical form (XRPD), deutivacaftor isotopic purity (%D9), microbial limits and water activity. The analytical procedures used are stability indicating.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Except for an increase in water content, which did not negatively impact tablet stability, the stability data showed no clear trends or changes in any of the tested parameters at all three storage conditions. All parameters remained within the specification limits. No clear degradation was observed and no degradation products were found above the ICH reporting threshold of 0.1%.

In addition, photostability was evaluated per ICH Q1B Option 2 on one batch of finished product per strength. No changes in appearance, assay, degradation products, enantiomeric impurities and isotopic purity were observed in the directly exposed samples. Results were comparable to the covered samples.

Forced degradation studies were conducted on 125 mg/50 mg/10 mg tablets exposed to thermal, thermal/humidity, treatment under acidic, basic, and oxidative conditions, and ultraviolet (UV) and visible light. Since both tablet strengths have the same core tablet composition and film coating system (with only minor differences in level of pigments), and both tablet strengths are manufactured using the same blend and the same dry granulation manufacturing process, the forced degradation conclusions from the 125 mg/50 mg/10 mg tablets are applicable to the tablets of lower strength. The results demonstrated that the vanzacaftor and tezacaftor/deutivacaftor finished product HPLC methods for assay and degradation product determination are stability indicating.

Bulk stability data have been provided on two batches per strength stored at 25°C/60% RH (24 months), 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The batches were packed in double LDPE bags inside a laminated foil bag. The batches were evaluated for appearance, assay, degradation products, chiral purity, dissolution, water content, physical form (XRPD), isotopic purity, water activity and microbial quality. No clear trends or changes were observed in any of the tested parameters at all three storage conditions. The claimed bulk hold time of 24 months when stored at or below 30°C is justified based on the presented bulk stability data. Compliance with the note for guidance on start of shelf-life of the finished dosage form has been confirmed.

Based on available stability data, the proposed shelf-life of 2 years with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

#### *2.3.5.5. Adventitious agents*

No excipients derived from animal or human origin have been used.

### 2.3.6. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The applicant leveraged prior knowledge from the development of authorised medicinal products containing ivacaftor and/or tezacaftor (e.g. Kalydeco, Orkambi) for the development of this new FDC tablets. QbD principles in the development of the active substance and finished product and their manufacturing process has been applied. Design spaces have been proposed for several steps in the manufacture of the active substances and finished product. The design spaces have been adequately verified. The major objections (MO) raised by the CHMP on the proposed starting materials for deutivacaftor and vanzacaftor and the nitrosamine risk evaluation were satisfactorily addressed. Overall, the results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

### 2.3.7. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.3.8. Recommendations for future quality development

n/a.

## *2.4. Non-clinical aspects*

### 2.4.1. Introduction

The applicant submitted non-clinical studies supporting the indication. New studies were performd mostly with VNZ and D-IVA. Data on tezacaftor and ivacaftor was previously assessed for Symkevi, Kalydeco and information has been summarised for these active substances. The details are presented below.

### 2.4.2. Pharmacology

#### *2.4.2.1. Primary pharmacodynamic studies*

*F508del-CFTR processing and trafficking in HBE cells*

Changes in the processing and trafficking of F508del-CFTR in response to treatment was measured in human bronchial epithelial (HBE) cells (Study T048). These cells were derived from a donor who was either

homozygous for F508del (F/F-HBE), or heterozygous for F508del and a minimal function CFTR mutation (F/MF-HBE). The MF CFTR allele tested was 3905insT, which does not produce CFTR protein and therefore cannot respond to CFTR modulators. F508del causes a severe defect in the CFTR protein processing and trafficking, resulting in little-to-no-mature F508del-CFTR at the cell surface. Changes in the processing and trafficking of F508del-CFTR were evaluated by Western blot analysis after 18-24 h treatment with TEZ+D-IVA, D-IVA+VNZ or TEZ+D-IVA+VNZ. Compound concentrations were as follows: 18 µM TEZ, 1 µM D-IVA and 220 nM VNZ.

In F/MF-HBE and F/F-HBE cells, minimal levels of mature, glycosylated CFTR protein were observed at steady-state. Treatment with VNZ in dual combination with D-IVA or in triple combination with D-IVA+TEZ resulted in increased levels of mature protein more than treatment with dual combination of D-IVA+TEZ, compared to vehicle-treated cells. In F/MF-HBE cells, the additive effect of TEZ in the triple combination was less pronounced compared to the effect in F/F-HBE cells.

These results demonstrate that VNZ is a CFTR corrector, and that TEZ+D-IVA+VNZ treatment results in increased processing and trafficking of the F508del-CFTR protein in CF-HBE cells with the F508del/F508del and F508del/MF genotype.

*F508del-CFTR-mediated Cl- transport in HBE cells*

Increased quantity and function of CFTR at the cell surface should result in increased CFTR activity in HBE cells, as measured by CFTR-mediated $Cl^-$ transport (Study S525). These cells were derived from a donor who was either homozygous for F508del (F/F-HBE), or heterozygous for F508del and a minimal function CFTR mutation (F/MF-HBE). The MF CFTR alleles tested were G542X, 3905insT and 1898+1G>A, each of which do not produce CFTR protein and therefore cannot respond to CFTR modulators. $Cl^-$ transport was evaluated by Ussing chamber electrophysiology after 18-24 h treatment with VNZ, VNZ+TEZ, VNZ+D-IVA or TEZ+D-IVA+VNZ. Compound concentrations were as follows: 18 µM TEZ, 1 µM D-IVA and concentration range of VNZ to determine the potency and efficacy of VNZ alone or in combination with the other modulators.

VNZ alone, in dual combination with TEZ or D-IVA, or in triple combination with TEZ+D-IVA, caused a concentration-dependent increase in $Cl^-$ transport in F/F-HBE cells and F/MF-HBE cells. These data suggest that the triple combination is more potent than the dual combinations, however the efficacy was similar between the triple combination and VNZ+D-IVA. The additive effect of TEZ was minimal at clinically equivalent concentrations (see Section 3.3.4.7.2 Analysis of the contribution of each compound to the clinical efficacy). VNZ in dual combinations with D-IVA or TEZ and in triple combination with D-IVA and TEZ was superior in efficacy to the dual combination of 1 µM IVA + 18 µM TEZ (Symkevi, mean Cl- transport was 21.5 µA/cm2 and 12.4 µA/cm2 in F/F and F/MF-HBE cells, respectively).

In conclusion, these data demonstrate that TEZ+D-IVA+VNZ treatment results in improved $Cl^-$ transport in CF-HBE cells with the F508del/F508del and F508del/MF genotype.

*N1303K-CFTR-mediated Cl- transport in HBE cells*

In addition, the *in vitro* response of N1303K-CFTR to VNZ/TEZ/D-IVA was tested in HBE cells derived from CF donors homozygous for N1303K or heterozygous for N1303K and a MF (1717-1G>A or c.1650delA) CFTR mutation (Study U020). $Cl^-$ transport was evaluated by Ussing chamber electrophysiology after 18-24 h treatment with TEZ+IVA, TEZ+IVA+ELX or TEZ+D-IVA+VNZ. Compound concentrations were as follows: 18 µM TEZ, 1 µM IVA, 1 µM D-IVA, 3.3 µM ELX and 220 nM VNZ.

The combination of VNZ/TEZ/D-IVA caused an increase in $Cl^-$ transport in N1303K/N1303K-HBE cells and N1303K/MF-HBE cells compared to TEZ/IVA and vehicle treated cells. This response was similar to cells

treated with ELX/TEZ/IVA. The mean $Cl^-$ transport was 10.0 µA/$cm^2$ (TEZ+IVA), 36.5 µA/$cm^2$ (TEZ+IVA+ELX) and 40.7 µA/$cm^2$ (VNZ+TEZ+D-IVA) in N1303K/N1303K-HBE cells and 7.1-8.2 µA/$cm^2$ (TEZ+IVA), 22.3-29.1 µA/$cm^2$ (TEZ+IVA+ELX) and 25.3-34.6 µA/$cm^2$ (VNZ+TEV+D-IVA) in N1303K/MF-HBE cells.

In conclusion, these data demonstrate that TEZ+D-IVA+VNZ treatment results in improved $Cl^-$ transport in CF-HBE cells with the N1303K/N1303K and N1303K/MF genotype.

*Estimation of VNZ concentrations in the CF-HBE cell model*

The applicant explained the calculation methods behind the correcting and comparison of the CF-HBE cell model results from the primary PD studies to the clinical situation. The results from the CF-HBE study, in order to compare them to the clinical concentrations, were corrected for the plasma protein binding. In human plasma the binding is >99%. The CF-HBE cell culture medium contains protein at concentrations that are ~25% of those in human plasma (20% added human serum and 5% additional proteins in the medium). In Method 1, the applicant divided the $C_{ave}$ measured clinically in CF patients by a factor 4 to correct for the difference in proteins.

This method for correction is considered less accurate than method 2, which is based on the actual measured free fraction in CF-HBE cells (Study T321). The clinically relevant concentrations in the CF-HBE model were 0.320 µM and 0.155 µM VNZ with method 1 and method 2, respectively. In the primary PD studies with CF-HBE, the applicant used either a fixed concentration of 220 nM VNZ, or a concentration range of VNZ to determine the $EC_{90}$ of VNZ in triple combination with TEZ+D-IVA in F/F-HBE and F/MF-HBE cells which resulted in 0.08 µM and 0.28 µM, respectively. In can be concluded that the primary PD studies in the CF-HBE model were conducted with clinically relevant concentrations of VNZ.

*In vitro pharmacological profiling of CFTR mutations in FRT cells*

In addition to the CF-HBE cell model, an *in vitro* transgenic Fischer rat thyroid (FRT) cell model was used to characterise the pharmacological response of additional CFTR mutations to VNZ/TEZ/D-IVA. Most *CFTR* gene mutations are rare, such that it is not practical to study each one in clinical studies. The FRT cell model is a cell model system that can be employed to characterise the responsiveness of *CFTR* mutations that produce at least some amount of full-length CFTR protein. Within this cell model, the function of CFTR at the cell surface in FRT cells expressing different mutant *CFTR* forms was directly assessed in Ussing chamber studies that quantify the amount of CFTR-mediated $Cl^-$ transport as a fraction of the $Cl^-$ transport in FRT cells expressing normal CFTR. A positive response was defined as a 10-percentage point (pp) increase in *in vitro* $Cl^-$ transport over baseline when expressed as a percentage of normal CFTR $Cl^-$ transport.

To identify VNZ/TEZ/D-IVA responsive mutations in the FRT assay, the applicant provided two *in vitro* studies. In the first study (Study P289, also part of Kaftrio indication extension procedure EMEA/H/C/005269/WS2551), 235 mutations were initially selected, and eventually the function of 219 non-*F508del*-CFTR mutations and the *F508del* mutation was assessed following 18-24 h treatment with IVA, IVA+TEZ or IVA+TEZ+ELX. A total of 15 *non-F508del* FRT cell lines failed the quality control (e.g. insufficient *CFTR* gene expression or incorrect gene sequence), including 2 mutations which are already included in the Kalydeco/Symkevi indication (*S1255P* and *R117C*); these latter 2 mutations are anyway labelled as IVA and IVA+TEZ responsive. Compound concentrations were as follows: 10 µM TEZ, 1 µM IVA and 10 µM ELX.

FRT cells expressing the *F508del* mutation did not respond to IVA or TEZ+IVA, but were responsive to IVA+TEZ+ELX (change from baseline: 25 pp). The non-responsiveness of the *F508del* mutation to IVA only (change over baseline: 3 pp) and TEZ+IVA (change over baseline: 5 pp) is in line with previous studies

conducted within the Symkevi application. Regarding the non-*F508del* mutations, 88 mutations were responsive to IVA, 148 mutations were responsive to TEZ+IVA, and 175 mutations were responsive to TEZ+IVA+ELX. All of the 88 IVA-responsive mutations were also responsive to the dual combination of TEZ+IVA. Likewise, all 148 mutations that responded to IVA and/or IVA+TEZ treatment, were also IVA+TEZ+ELX responsive.

In the following *in vitro* study using the FRT system (Study U015), 475 *CFTR* mutations that produce full-length CFTR protein and met one of the following criteria were selected for the study: (1) *CFTR* mutations previously shown to be responsive to ELX/TEZ/IVA, but not responsive to IVA or TEZ/IVA (from Study P289); (2) *CFTR* mutations which were not responsive to ELX/TEZ/IVA (from Study P289); (3) *CFTR* mutations not previously tested in the FRT cell model. The function of 474 non-*F508del*-CFTR mutations and the *F508del* mutation was assessed following 18-24 h treatment with VNZ+TEZ+D-IVA. Compound concentrations were as follows: 10 μM TEZ, 1 μM D-IVA and 3 μM VNZ. The concentration used for VNZ was based on the $EC_{90}$ for VNZ in combination with D-IVA+TEZ in F508del-FRT cells. This is ~10-fold higher compared to the $EC_{90}$ for VNZ in combination with D-IVA+TEZ in MF-HBE cells (=0.28 μM, Study S525), which was considered a clinical equivalent concentration. VNZ+TEZ+D-IVA increased $Cl^-$ transport in FRT cells expressing *F508del*-CFTR (change from baseline: 136 pp). Regarding the non-*F508del* mutations, 420 out of 474 mutations were responsive to VNZ/TEZ/D-IVA, and a subset of 54 mutations was not responsive to VNZ/TEZ/D-IVA. Of the 420 responsive *CFTR* mutations, 47 were responsive to VNZ+TEZ+D-IVA but not ELX+TEZ+IVA.

*F508del- and non-F508del-CFTR processing and trafficking in FRT cells*

In addition to measuring functional response in the *in vitro* FRT system, the effect of VNZ+TEZ+D-IVA on the processing and trafficking of mutant CFTR protein was assessed via Western blot (Study U015). The amount of mature and immature CFTR protein of 160 non-*F508del*-CFTR mutations and the *F508del* mutation was assessed following 18-24 h treatment with VNZ+TEZ+D-IVA. Compound concentrations were as follows: 10 μM TEZ, 1 μM D-IVA and 10 μM VNZ.

At baseline, the 161 evaluated mutations demonstrate a wide range of mature CFTR protein expression, since the mutant CFTR forms are known to cause a range in the severity of the defect in CFTR processing and trafficking. In general, VNZ+TEZ+D-IVA treatment resulted in increased mature CFTR protein expression in most of the tested FRT cell lines, which is to be expected based on the well-characterised mechanism of action.

The list of currently known VNZ/TEZ/D-IVA responsive FRT mutations is provided below and inserted in section 5.1 of the SmPC.

**Table 3. CFTR mutations identified to be responsive to D-IVA/TEZ/VNZ based on clinical and/or in vitro data**

| | | | | |
|---|---|---|---|---|
| 1140-1151dup | E116Q | H147del | N1088D | S1118F |
| 1461insGAT | E1221V | H147P | N1195T | S1159F* |
| 1507_1515del9 | E1228K | H199Q | N1303I | S1159P# |
| 2055del9 | E1409K | H199R | N1303K¶ | S1188L |
| 2183A→G | E1433K | H199Y | N186K | S1251N* |
| 2789+5G→A† | E193K# | H609L | N187K | S1255P |
| 2851A/G | E217G | H609R | N396Y | S13F |
| 293A→G | E264V | H620P | N418S | S13P |
| 3007del6 | E282D | H620Q | N900K | S158N |
| 3131del15 | E292K | H939R# | P1013H | S182R |
| 3132T→G | E384K | H939R; | P1013L | S18I |
| 3141del9 | E403D# | H949L‡ | P1021L | S18N |
| | E474K | H954P | P1021T | S308P |

| | | | | |
|---|---|---|---|---|
| 3143del9 | E527G | I1023R | P111L | S341P |
| 314del9 | E56K[#] | I105N | P1372T | S364P |
| 3195del6 | E588V[#] | I1139V[#] | P140S | S434P |
| 3199del6 | E60K[#] | I1203V | P205S[#] | S492F |
| 3272-26A→G[†] | E822K[#] | I1234L | P439S | S50P |
| 3331del6 | E831X[†] | I1234Vdel6aa | P499A | S519G |
| 3410T→C | E92K[#] | I125T | P574H | S531P |
| 3523A→G | F1016S[#] | I1269N[#] | P5L[#] | S549I |
| 3601A→C | F1052V[#] | I1366N[#] | P67L[#] | S549N[*] |
| 3761T→G | F1074L[#] | I1366T | P750L | S549R[*] |
| 3791C/T | F1078S | I1398S | P798S | S557F |
| 3849+10kbC→T[†] | F1099L[#] | I148L | P988R | S589I |
| 3850G→A | F1107L | I148N | P99L | S589N[#] |
| 3978G→C | F191V[#] | I148T; | Q1012P | S624R |
| 4193T→G | F200I | H609R[‡] | Q1100P | S686Y |
| 546insCTA[#] | F311del[#] | I175V[#] | Q1209P | S737F[#] |
| 548insTAC | F311L[#] | I331N | Q1291H | S821G |
| 711+3A→G[†] | F312del | I336K[*] | Q1291R[#] | S898R |
| A1006E[#] | F433L | I336L | Q1313K | S912L[#] |
| A1025D | F508C;S1251N[‡ #] | I444S | Q1352H | S912L; |
| A1067P | F508del[*] | I497S | Q151K | G1244V[‡] |
| A1067T[#] | F508del;R1438W[‡] | I502T[*] | Q179K | S912T |
| A1067V | F575Y[#] | I506L | Q237E[#] | S945L[*] |
| A107G | F587I | I506T | Q237H[#] | S955P |
| A1081V | F587L | I506V | Q237P | S977F[#] |
| A1087P | F693L(TTG) | I506V; | Q30P | S977F; |
| A120T[#] | F87L | D1168G[‡] | Q359K/T360K[‡] | R1438W[‡] |
| A1319E | F932S | I521S | Q359R[#] | T1036N[#] |
| A1374D | G1047D | I530N | Q372H | T1057R |
| A141D | G1047R | I556V | Q452P | T1086A |
| A1466S | G1061R | I586V | Q493L | T1086I |
| A155P | G1069R[#] | I601F[#] | Q493R | T1246I |
| A234D[#] | G1123R | I601T | Q552P | T1299I |
| A234V | G1173S | I618N | Q98P | T1299K |
| A238V | G1237V | I618T[#] | Q98R[#] | T164P |
| A309D | G1244E[*] | I86M | R1048G | T338I[#] |
| A349V[#] | G1244R | I980K[#] | R1066C | T351I |
| A357T | G1247R | K1060T[#] | R1066G | T351S |
| A455E[*] | G1249E | K162E | R1066H[*] | T351S;R851L[‡] |
| A455V | G1249R[#] | K464E | R1066L | T388M |
| A457T | G1265V | K464N | R1066M | T465I |
| A462P | G126D[#] | K522E | R1070P | T465N |
| A46D | G1298V | K522Q | R1070Q[#] | T501A |
| A534E | G1349D[#] | K951E | R1070W[#] | T582S |
| A554E[#] | G149R | L1011S | R1162Q | T604I |
| A559T | G149R;G576A;R668C[‡] | L102R | R117C | T908N |
| A559V | G178E[#] | L102R; | R117C; | T990I |
| A561E | G178R[#] | F1016S[‡] | G576A; | V1008D |
| A566D | G194R[#] | L1065P | R668C[‡] | V1010D |
| A613T | G194V[#] | L1065R | R117G[#] | V1153E[#] |
| A62P | G213E | L1077P[*] | R117H | V11I |
| A72D | G213E;R668C[‡] | L1227S | R117L[#] | V1240G[#] |
| A872E | G213V | L1324P[#] | R117L;L997F[‡] | V1293G[#] |
| c.1367_1369dupTTG | G226R | L1335P[#] | R117P[#] | V1293I |
| C225R | G239R | L137P | R1239S | V1415F |
| C491R | G253R | L137R | R1283G | V201M[#] |
| C590Y | G27E | L1388P | R1283M[#] | V232A |
| C866Y | G27R | L1480P[#] | R1283S[#] | V232D[#] |
| | | L159S | R1438W | V317A |

| | | | | |
|---|---|---|---|---|
| D110E[#] | G314E[#] | L15P[#] | R248K | V322M |
| D110H[#] | G314R | L15P;L1253F[‡] | R258G[#] | V392G |
| D110N | G424S | L165S | R297Q | V456A |
| D1152A | G437D | L167R | R31L[#] | V456F |
| D1152H[*] | G451V | L206W[*] | R334L[#] | V520F |
| D1270N[#] | G461R | L210P | R334Q[#] | V520I |
| D1270Y | G461V | L293P | R347H[#] | V562I;A1006[‡] |
| D1312G | G463V | L327P | R347L[#] | V562L |
| D1377H | G480C | L32P | R347P[*] | V591A |
| D1445N | G480D | L333F | R352Q[*] | V603F |
| D192G[#] | G480S | L333H | R352W[#] | V920L |
| D192N | G500D | L346P[#] | R516G | V920M |
| D373N | G545R | L441P | R516S | V93D |
| D426N | G551A | L453S | R553Q[#] | W1098C[*] |
| D443Y[#] | G551D[*] | L467F | R555G | W1282G |
| D443Y;G576A;R668C[‡ #] | G551R | L558F | R560S | W1282R[*] |
| D513G | G551S[#] | L594P | R560T | W202C |
| D529G | G576A;R668C[‡#] | L610S | R600S | W361R |
| D565G | G576A;S1359Y[‡] | L619S | R709Q | W496R |
| D567N | G622D[#] | L633P | R74Q[#] | Y1014C[#] |
| D572N | G622V | L636P | R74Q;R297Q[‡] | Y1032C[#] |
| D579G[#] | G628A | L88S | R74Q;V201M;D1270N[‡] | Y1032N |
| D58H | G628R | L927P | R74W[#] | Y1073C |
| D58V | G85E[*] | L967F;L1096R[‡] | R74W;D1270N[‡ #] | Y1092H |
| D614G[#] | G85V | L973F | R74W;R1070W;D1270 | Y109C |
| D651H | G91R | M1101K[*] | N[‡] | Y109H |
| D651N | G930E | M1101R | R74W;S945L[‡] | Y109N[#] |
| D806G | G970D[#] | M1137R | R74W;V201M[‡#] | Y122C |
| D924N[#] | G970S | M1137V | R74W;V201M;D1270N | Y1381H |
| D979A | G970V | M1210K | [‡#] | Y161C |
| D979V[#] | H1054D[*] | M150K | R74W;V201M;L997F[‡] | Y161D |
| D985H | H1079P | M150R | R751L[#] | Y161S[#] |
| D985Y | H1085P | M152L | R75L | Y301C |
| D993A | H1085R | M152V[#] | R75Q;L1065P[‡] | Y517C |
| D993G | H1375N | M265R[#] | R75Q;N1088D[‡] | Y563N[*] |
| D993Y | H1375P[#] | M348K | R75Q;S549N[‡] | Y569C |
| E1104K | H139L | M394L | R792G[#] | Y89C |
| E1104V | H139R | M469V | R792Q | Y913C |
| E1126K | H146R | M498I | R810G | Y913S |
| E116K[#] | | M952I[#] | R851L | Y919C |
| | | M952T[#] | R933G[#] | |
| | | M961L | S1045Y | |
| | | | S108F | |

[*] Mutations supported by clinical data.
[†] Non-canonical splice mutations where efficacy is extrapolated from clinical data from other CFTR modulators because these mutations are not amenable to FRT assay.
[‡] Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.
[¶] N1303K is extrapolated from clinical data from IVA/TEZ/ELX in combination with IVA and supported by Human Bronchial Epithelial (HBE) assay data.
[#] Mutations are extrapolated from FRT data with TEZ/IVA or IVA monotherapy in which a positive response is indicative of a clinical response.

Non-annotated mutations are included based on the FRT assay with D-IVA/TEZ/VNZ in which a positive response is indicative of a clinical response.

The list of Alyftrek nonresponsive mutations is provided below in Table 4.

**Table 4. CFTR mutations that did not show a positive response in the vitro FRT test**

| | | | | |
|---|---|---|---|---|
| 1234insACAAAA | c.1493-1507del15 | I506S | M1105R | S489P |
| 1491-1500del | C524R | I507del | M1137K | V1020E |
| 149del84 | C832X | K95E | M156R | W1098R |
| 1949del84 | D565E | L102P | M1L | W277X |
| 2862delCAG | D579Y | L127dup | M1T | W57G |
| 2949del84 | E815X | L227R | M1V | W57R |
| 420del9 | G1003E | L467P | M394R | Y563D |
| 591del18 | G458R | L558S | N1303K | Y563H |
| A1067D | G85R | L571S | R334W | Y569D |
| A559E | G921E | L617del | R560G | Y914C |
| A559P | I1005R | L73P | R560K | |

***Secondary pharmacodynamic studies***

*VNZ*

VNZ was tested in an *in vitro* radioligand binding assay at a concentration of 1 µM against a broad panel of 177 protein targets. Data from this assay showed significant binding inhibition (≥50%) at adrenergic α1a (71%), α1b (81%), and PGI2 (51%). Follow up assays resulted in IC50 values of 8.6 µM, 13.5 µM and 1.45 µM, respectively. This is well above the clinical concentrations (>266-fold margin of exposure) and the proposed therapeutic dose of 20 mg once daily (free Cmax: 0.184 nM), and therefore not considered relevant.

*D-IVA*

Secondary PD studies were performed to compare IVA with D-IVA, showing similar results and therefore no additional off-target effects are expected with D-IVA.-

*IVA*

Safety pharmacology studies for IVA were submitted and assessed with the previous MAA procedures for Kalydeco and Symkevi.

IVA was evaluated for potential off-target effects in a panel of 168 *in vitro* receptor, channel, and enzyme radioligand binding assays. IVA appeared to stimulate the monoamine transporter and the serotonin receptor (5-HT2C) at sub-micromolar potency. Since IVA has a low potency to cross the blood-brain-barrier, interaction with these targets was considered unlikely upon treatment of patients. Based on Studies 106 and 107, the IVA $C_{max}$ of 1.20 mg/l is obtained under steady-state conditions when given 150 mg OD. With >99% protein bound, the free IVA $C_{max}$ is 0.012 mg/ml, which equals 0.03 µM. Thus, no secondary pharmacology effects of IVA are anticipated in human. Two IVA metabolites are substantially present in human, M1 and M6. In plasma, IVA and its major circulating metabolites IVA-M1 and IVA-M6 accounted for 12%, 66% and 21%

of $AUC_{inf}$. Of these IVA-M1 was pharmacologically active with a 6-fold lower potency than IVA. Mean $EC_{50}$ value was 1.2 µM for IVA-M1 and 0.2 µM for IVA.

*TEZ*

Secondary pharmacology studies for TEZ were submitted and assessed with the previous MAA procedures for Kalydeco and Symkevi.

TEZ was evaluated for potential off-target effects in a panel of 168 *in vitro* receptor, channel, and enzyme radioligand binding assays. TEZ showed only significant binding affinity to the sodium channel Site 2 target receptor at concentrations below 10 µM (Ki = 6.6 µM). However, in a functional assay no significant binding to any of the NaV channels; NaV1.1, NaV1.3, NaV1.5, NaV1.7, and NaV1.8, could be determined. Based on Studies 106 and 107, a TEZ $C_{max}$ Assessment report EMA/CHMP/567306/2018 Page 34/165 of 6 mg/l is obtained under steady-state conditions when given 100 mg OD to CF patients. With >99% protein bound, the free TEZ $C_{max}$ is 0.06 mg/ml, which equals to 0.11 µM. Thus, no secondary pharmacology effects of TEZ are anticipated in human.

Three TEZ metabolites are substantially present in human, TEZ-M1, TEZ-M2, and TEZ-M5. In plasma, TEZ and its major circulating metabolites TEZ-M1, TEZ-M2 and TEZ-M5 accounted for 7%, 15%, 31% and 33% of AUC values of the total radioactivity, respectively. TEZ-M3 accounted for 7% of the total radioactivity AUC. Of these, only TEZ-M1 appears pharmacologically active. The potency of TEZ-M1 and TEZ in the presence of continuous IVA in Cultured F/F- (F508del) HBE Cells were similar with $EC_{50}$ values of 3.24 µM for TEZ-M1 and 5.95 µM for TEZ.

### *2.4.2.2. Safety pharmacology programme*

*VNZ*

A comprehensive programme of safety pharmacology studies was conducted with VNZ.

VNZ inhibited hERG current with an IC50 of 0.7 µM, which provides a ~3800-fold margin of exposure over the clinical concentration (free Cmax). Effects of VNZ on the cardiovascular system was assessed in telemetered male dogs. A single dose of VNZ at up to a dose of 4 mg/kg did not result in any changes in cardiovascular parameters. Therefore, the NOEL for cardiovascular effects was considered 4 mg/kg (mean plasma concentration = 7133 ng/mL), resulting in a ~9-fold exposure margin.

The effects of VNZ on the CNS and the respiratory system were assessed after a single dose administration in female rats. Up to a dose of 10 mg/kg, no effects on clinical observations, neurobehavioral endpoints, respiratory effects or unscheduled deaths were observed. No toxicokinetic parameters were assessed in this study, but when comparing to the exposure from the 28-day repeat-dose toxicity studies in rats, sufficient exposure margins were obtained (~35-fold).

*D-IVA*

D-IVA inhibited hERG current with an IC20 of 0.86 µM, which provides a ~200× margin of exposure over the proposed therapeutic dose of 250 mg once daily (free Cmax: 4.25 nM).

No stand-alone in vivo safety pharmacology studies were conducted, and safety pharmacology parameters were included in repeat-dose toxicity studies with D-IVA. In addition, a 13-week repeat-dose bridging study with D-IVA and IVA was performed (see section 4.2). This is acceptable.

*IVA*

Safety pharmacology studies for IVA were submitted and assessed with the previous MAA procedures for Kalydeco and Symkevi.

IVA inhibited hERG channel ($IC_{15}$ of 5.5 µM), Cav1.2 ($IC_{50}$ of 1.3 µM) and Kv1.5 ($IC_{50}$ of 3.4 µM). IVA-M6 (10 µM) showed only minimal inhibition of hCav1.2, hKvLQT1/minK, and hNav1.5 (in CHO cells) or hERG and hKir2.1. As the unbound/ free fraction of IVA in human serum is 0.03 µM, the inhibition of hERG and other channels influencing cardiac currents, is not regarded as clinically relevant.

IVA had no effect on CNS or respiratory function in Sprague Dawley rats. Cardiovascular examination revealed a dose-related, but transient increase in the ABP parameters (SBP, DBP, and MAP) at 60 minutes post dose, but was considered non-adverse due to the small magnitude and brief nature of the response (Assessment report EMA/CHMP/567306/2018 Page 35/165). Fasted Sprague Dawley Rats administered a single dose of 250, 500 or 1000 mg/kg ivacaftor showed statistically significant increases in stomach plus content weight and in GI transit time. Overall, results from safety pharmacology studies evaluating IVA and of the secondary pharmacodynamic screening studies suggest a high degree of selectivity and a low potential to have biologically meaningful effects on vital function when IVA is administered in combination.

*TEZ*

Safety pharmacology studies for TEZ were submitted and assessed with the previous MAA procedures for Kalydeco and Symkevi.

TEZ ($IC_{50}$ > 10 µM) and TEZ-M2 ($IC_{50}$ > 200 µM) are not considered potent hERG inhibitors and as the clinical free fraction of TEZ is 0.11 µM, the hERG channel inhibition by TEZ is not regarded clinically relevant.

TEZ had no effect on CNS or respiratory function in Sprague Dawley rats dosed 0, 20, 60 or 200 mg/kg. Cardiovascular examination revealed increased ABP (17 to 25%) and decreased QT and QTc intervals (2 to 8%) between 6 to 14 hours after oral administration in 2/4 dogs dosed 250 mg/kg. Since in human, QTc effects were not noted, this observation is not regarded as clinically relevant. Fasted Sprague Dawley Rats administered 100 or 200 mg/kg TEZ once daily by oral gavage for 4 days, showed significantly delayed gastric emptying of the charcoal test meal, but this effect was not observed in the clinical study. Overall, results from safety pharmacology studies evaluating TEZ and of the secondary pharmacodynamic screening studies suggest a high degree of selectivity and a low potential to have biologically meaningful effects on vital function when TEZ is administered in combination.

#### *2.4.2.3. Pharmacodynamic drug interactions*

No dedicated pharmacodynamic drug interactions studies are submitted. This can be agreed since all components are very specific for CFTR and it is not anticipated that they will be administered with another therapy directly affecting CFTR.

## 2.4.3. Pharmacokinetics

The applicant presented a good amount of pharmacokinetic data for VNZ, since this is a new compound. For D-IVA data was presented and compared to IVA data. For TEZ the applicant mainly referred to the Symkevi dossier. A new, GLP compliant, combination study in rats was performed with one fixed combination of all three compounds, as well as combination treatment of VNZ and D-IVA and single treatment with VNZ, D-IVA

and TEZ. Metabolites M1-D-IVA and M6-D-IVA were measured, since M1-IVA and M6-IVA are both known major human metabolites of ivacaftor.

**Analytical methods**

The applicant provided validation reports for the analytical methods used, demonstrating the suitability of the methods, storage and handling of D-IVA and its metabolites (M1-D-IVA and M6-D-IVA) and VNZ. Analytical methods for TEZ and metabolites and IVA and metabolites were also already validated as part of the Symkevi MAA dossier.

The facilities where the validation studies were performed are both OECD GLP-compliant facilities. TEZ was validated previously as part of previous product MAAs.

The applicant provided validation reports for the analytical methods used, demonstrating the suitability of the methods, storage and handling for the purpose of analysis of TEZ and its metabolites (M1-TEZ and M2-TEZ). Specific and sensitive bioanalytical assays have been developed and validated for the quantitative determination of these compounds in rat, mouse, rabbit and dog plasma. In these methods, biological samples were extracted by liquid–liquid extraction (GLP studies) or by protein precipitation (non-GLP studies) and analysed by LC-MS/MS with stable isotope labelled analogues of the analytes used as internal standards. The assay reproducibility was demonstrated at least once per species / per assay using an incurred samples reanalysis approach during sample analysis.

The radiochemical procedures (QWBA, LSC and radiometric detector attached to HPLC) used to detect $^{14}$C-VNZ, $^{14}$C-TEZ, $^{14}$C-D-IVA and $^{14}$C-IVA are adequate.

**Absorption**

*In vitro* permeability

*In vitro* studies in Caco-2 cells and MDCK-MDR1 showed that VNZ has a low to moderate permeability and is not a substrate for P-gp. D-IVA has a profile similar to IVA, with a moderate permeability. TEZ showed a high permeability in Caco-2 cells. Both D-IVA (and IVA) and TEZ are substrates for P-gp.

VNZ pharmacokinetics

Absorption kinetics of the new chemical compound vanzacaftor have been extensively characterised in non-clinical animal studies. Studies were performed in mice, rats, rabbits, dogs and monkeys. Most data was collected in the toxicology studies or in dose range finding studies for the pivotal toxicity studies.

Differences between animal species are observed in bioavailability of vanzacaftor in single dose studies. Using the same oral formulation, bioavailability in rats was highest at 76.9%, followed by dogs with 49.7% and monkeys with only 12.9%. No bioavailability data was reported for rabbits and mice. Absolute bioavailability of VNZ in humans was not measured, but relative bioavailability increased with a high-fat meal in humans.

In human healthy subjects VNZ $AUC_{0-\infty}$ ranged from 3.90-35.1 ug*h/mL in different studies, depending on dose and formulation. At clinical dose, combined with D-IVA and TEZ, the $AUC_{0-\infty}$ was 18.0 ug*h/mL. This range, including multiples of this exposure, appears to have been adequately covered in the non-clinical evaluation of the VNZ pharmaco- and toxicokinetics. In rats, in the combination study, VNZ AUC ranged from 17.2 to 164 ug*h/mL. In other, monotherapy, studies in rats AUCs ranged from 1.82 to 2620 ug*h/mL. In dogs, AUCs ranged from 2.78 to 2080 ug*h/mL over different dosages and studies. Clearance was determined after IV administration in mice (3.12 mL/min/kg), in rats (1.06 mL/min/kg), in dogs (0.227 mL/min/kg) and monkeys (2.98 mL/min/kg). Clearance in humans was 1.18 L/h (0.28 mL/min/kg). $t_{1/2}$ was

shorter in non-clinical species than in humans. In mice 6.34 hours, in rats 19.2 hours, in dogs 12.4 hours, and in monkeys 2.09 hours after intravenous administration. In humans $t_{1/2}$ was 54.0 hours. Therefore, it appears the clearance is slow in humans with a long half-life (>2-fold) compared to non-clinical animal species.

For VNZ no substantial sex differences were seen in non-clinical species. Accumulation of VNZ over time was seen in all animal species. In mice a 2-fold accumulation in AUC was seen after 26 weeks. In rats there was a 2-3 fold accumulation over 26 weeks administration and in dogs the accumulation over 39 weeks was about 3-fold for the low dose, was about 4-fold for the highest tested dose. Overall, exposure in mice, rats, rabbits and dogs appears to increase in a more-than-dose-proportional manner in most studies, however, substantially disproportional increases were not observed.

D-IVA pharmacokinetics

For D-IVA, kinetic studies have been performed in mice, rats and dogs. No studies were performed in rabbits and monkeys. Kinetics of major human metabolite M1-D-IVA and M6-D-IVA were also assessed in rats and dogs. In all three NC animal species studied, IVA (and in rats also M1-IVA and M6-IVA) was also studied to enable a direct comparison of the PK data between D-IVA and IVA in order to bridge some of the IVA toxicology and pharmacology findings to D-IVA.

In CD-1 mice, single dose IV (2.5 mg/kg) and PO (10 mg/kg) doses of D-IVA and IVA were administered. Half-life was short and comparable at 2-3 hours for both D-IVA and IVA. After IV dosing, exposure was very similar between IVA and D-IVA. After PO administration, AUC of D-IVA was approx. 25% higher for D-IVA compared to IVA. The half-life and $C_{max}$, however, were very similar (marginally lower for D-IVA compared to IVA). The bioavailability of D-IVA was higher than for IVA (54% versus 39%), likely due to D-IVA's lower first pass metabolism.

In 28-day and 13-week rat studies, the exposure of males and females to D-IVA and IVA was similar, with a trend towards higher exposures in females. However, for the metabolites M1-D-IVA, M1-IVA, and especially M6-D-IVA and M6-IVA, exposures in males were higher than in females at all timepoints, with differences in AUC up to approx. 5-fold. Between day 1 and day 91 an increase in exposure of approx. 3-fold was seen for D-IVA (both sexes), approx. 7-fold for M1-D-IVA (both sexes) and up to a 20-fold increase in M6-D-IVA (both sexes). Overall, increases in dose resulted in slightly less-than-dose-proportional increases in AUC for D-IVA, M1-D-IVA and M6-D-IVA in both sexes.
For IVA, accumulation over time based on AUC was less, with approx. 1.5-fold (males) and 2.5-fold (females) between day 1 and day 85. For M1-IVA accumulation was approx. 3.5-fold (males) and 5.5-fold (females) and for M6-IVA accumulation was approx. 11-fold for both sexes.

In Beagle dogs, after a single PO administration (3 mg/kg) the AUC for D-IVA was ~1.8-fold higher compared to the AUC for IVA, as was also observed in rats. In dogs $t_{1/2}$ was slightly higher for D-IVA compared to IVA and also the $C_{max}$ was higher for D-IVA (~1.6-fold) compared to IVA. No sex differences in exposure were observed in the 28-day dog study for D-IVA, M1-D-IVA and M6-D-IVA. Slight accumulation based on AUC was observed between day 1 and day 28, with accumulation of approx. 1.5-fold for D-IVA, 2-fold for M1-D-IVA and 2.5-fold for M6-D-IVA. Overall, increases in dose resulted in less-than-dose-proportional increases in AUC for D-IVA, M1-D-IVA and M6-D-IVA.

From a non-clinical point of view there does not seem to be a substantial difference between absorption parameters for D-IVA and IVA. Clinical pharmacokinetics may, however, still support the once daily dosing regimen. Human ivacaftor half-life (according to the Symkevi SmPC) is 9.3 hours, and the D-IVA half-life in healthy volunteers was 17.3 hours (FDC tablets).

From a non-clinical point of view there does not seem to be a substantial difference between absorption parameters for D-IVA and IVA.

TEZ pharmacokinetics

PK studies in mice, rats, rabbits, dogs and cynomolgus monkeys were previously conducted for TEZ, and/or M1-TEZ and/or M2-TEZ via oral, intravenous or subcutaneous administration to support the registration of Symkevi. The key aspects are described below:

In mice, after single administration, tezacaftor was orally well absorbed and exhibited low clearance (12.4 ml/min/kg) and a moderate volume of distribution (1.56 L/kg). The plasma exposure for M1-TEZ and M2-TEZ was 166% and 12.5% relative to TEZ, respectively. After repeated administration in mice, there was a decrease of the systemic exposure to tezacaftor in males and females, likely due to enzyme induction. At steady state, the exposure to M1-TEZ and M2-TEZ was ~4.2-6.0x and ~0.24-0.40x relative to TEZ especially at the higher dose levels.

The pharmacokinetic pattern in rats followed a similar pattern as in mice. In rats, after single oral administration, tezacaftor was orally good absorbed (bioavailability of 53%) and exhibited low clearance (7.21 ml/min) and a moderate volume of distribution (1.93 ml/min/kg). The increase in systemic exposure was dose-proportional over the dose range 9.25 to 203 mg/kg, and less than dose proportional at the 600 mg/kg dose level. The dose proportional increase in Cmax and AUC values over the dose range of 9.25 to 203 mg/kg and the consistent t1/2 estimates in the same range indicate linear kinetics in the disposition of tezacaftor from 9.25 to 203 mg/kg. M1-TEZ and M5-TEZ were the major circulating metabolites in rats, with systemic exposures relative to parent approximately 1.3-fold and 0.75-fold, respectively. M2-TEZ exposure was low and only approximately 0.05-fold relative to parent.

After repeated administration in rats (7 day-, 1 month-, 3 month-, 6 month-, 12-mounth studies), the exposure of tezacaftor generally increased as the dose increased. The increase in exposure was dose proportional at lower dose levels from 20 to 200 mg/kg/day or 100 mg/kg/day, dependent on study duration, and was less-than-dose-proportional at higher dose levels. No apparent accumulation of tezacaftor was observed, with the exception of the 52-week study at lower dose levels where 2-3 fold accumulation of tezacaftor. No meaningful sex-related differences were observed. Increases in tezacaftor doses led to an increase of M1-TEZ and M2-TEZ exposures in a dose proportional manner. Accumulation of these metabolites was observed in the 26- and 52-week studies. In pregnant rats, the systemic exposure to tezacaftor was similar to non-pregnant rats at steady state.

Toxicokinetic studies were performed in pregnant and non-pregnant rabbits to assess the exposure to tezacaftor the rabbit reproduction toxicity studies. These 2-week studies showed that repeated administration led to a dose-related exposure to tezacaftor. There was some evidence of accumulation of tezacaftor and TEZ-M1, but of M2-TEZ, in pregnant rabbits.

In dogs, after single oral administration, tezacaftor was well absorbed (bioavailability of 43%) and exhibited a low clearance (1.95 ml/min/kg) and a low volume of distribution (0.48 L/kg). The increase in systemic exposure was dose-proportional over the tested dose range (3 to 300 mg/kg). M2-TEZ is a major circulating metabolite in humans. Intravenous administration of M2-TEZ resulted in systemic plasma clearance of 1.32 mL/min/kg. The volume of distribution at steady state was low and the T½ was moderate, with respective values of 0.443 L/kg and 8.01 hr.

After repeated administration in dogs (7-day-, 28-day-, 3-month-, 6-month- and 12-month studies) the exposure of tezacaftor and the metabolites M1-TEZ or M2-TEZ increased dose proportional in the tested dose

range of 25 to 200 mg/kg/day. In general, no apparent accumulation was noted with tezacaftor or with the metabolites M1-TEZ or M2-TEZ. In addition, there was no evidence for sex difference or evidence for enzyme induction. The absorption of tezacaftor may be improved by the intake of food. In an 28-day investigative toxicity study in dogs, it was found that the exposure to tezacaftor, M1-TEZ and M2-TEZ at the 100 mg/kg/day dose in the fed group was similar to the exposure observed at the 250 mg/kg/day in the fasted group suggesting that there was a food effect in the study.

Combination studies

A GLP combination study with VNZ/TEZ/D-IVA was performed in rats. In this 13-week study one dose was used per compound: 2.5 mg/kg VNZ, 45 mg/kg TEZ and 17.5 mg/kg D-IVA. A control group that received vehicle was also included. 10 animals/sex/group were used. Triple therapy, VNZ/D-IVA combination and single compounds were tested. M1-TEZ, M2-TEZ, M1-D-IVA and M6-D-IVA were also measured in the plasma. Measurements were performed on Day 1, Day 28 and Day 91.

$AUC_{0\text{-}24h}$ values for VNZ, TEZ and D-IVA, whether administered alone or in combination remained generally similar. Combination of the substances did not influence their exposure. It was not reported whether there are shifts between bound/unbound fractions of compounds. For the measured metabolites there is some fluctuation in profiles between the mono- and combination therapies . M2-TEZ and M1-D-IVA appear to be formed less in combination treatments. M6-D-IVA may be formed more. This may be due to CYP metabolism and capacity in combination versus mono therapy. However, the AUC and $C_{max}$ values for the combination therapy all remain within a 2-fold margin compared to mono therapy. Therefore, these trends are unlikely to be relevant. There were no substantial (>2-fold) sex differences observed, except for M6-D-IVA, where exposure of males > females by approx. 2.5-10 fold. Interestingly, this sex difference disappeared in the triple therapy group, where exposure in females > males by 1.5-2 fold. Why the sex difference disappears in this specific group was not further discussed.

**Distribution**

Plasma protein binding was assessed *in vitro* by equilibrium dialysis for all three compounds. Protein binding of tezacaftor is high (>98%) plasma and similar across species. M1-TEZ, M2-TEZ and M5-TEZ are also highly bound to plasma proteins and similar across species (>97.5%), except M2-TEZ which is less protein bound in mouse plasma (93.6%). These protein binding percentages were independent of concentration, indicating that no saturation of binding was evident up to 10 µM. Vanzacaftor was also highly plasma protein bound (>99.9%) in all species, including humans. Plasma protein binding of D-IVA was assessed in rat, dog and human serum. Binding was >99% for all species including humans. M1-D-IVA and M6-D-IVA also showed a high binding of >99%, but this was only assessed in human plasma. Given the high plasma binding of all three compounds, equilibrium dialysis may not be the most accurate method to measure *in vitro* plasma protein binding. However, this method was also used in previous applications.

Blood:plasma partitioning in rats showed minimal association of radioactivity to the cellular components of the blood for VNZ and TEZ. *In vitro* studies showed also minimal distribution to red blood cells for D-IVA, M1-D-IVA and M6-D-IVA.

Tissue concentrations of VNZ were determined at 1, 4, 24 and 168 hours postdose in SD rats, and at 1, 2, 4, 8, 24, 72, 96, 168, and 672 hours postdose in LE rats using quantitative whole-body autoradiograph (QWBA). VNZ distributes to the lungs of Long-Evans rats, with measurable concentrations up to 72 hours, with concentrations lower than plasma levels especially at the earlier timepoints post-dose. Lung:plasma ratios ranged from 0.62-0.94. Concentrations were very high in stomach wall (only at the 1h and 2h time points), bile and liver tissues compared to plasma concentrations, which is explained by the metabolism and excretion

pathways. In SD rats the lung concentrations of VNZ were all below the plasma concentrations at all time points, with lung:plasma ratios of 0.68-0.75. After 168 hours, in SD rats, small amounts of VNZ were still present in cecum and large intestine, kidney tissues, bile duct, liver and nasal turbulates. In all other tissues the concentrations were BQL. In Long-Evans rats, at 672 hours, small amounts were still found in cecum, small intestine wall, ex-orbital lachrymal gland and liver. All other tissue concentrations were BQL.

Tissue concentrations of D-IVA and IVA were determined in SD rats (n=6) and LE rats (n=6) using quantitative whole-body autoradiograph (QWBA). Distribution to lung was seen in all groups. Distribution of D-IVA to lungs was slightly better than of IVA with lung:cardiac blood ratios of 4.25 in SD rats and 4.61 in LE rats for D-IVA compared to 3.5 in SD rats and 3.85 in LE rats for IVA. Otherwise, distribution was similar between D-IVA and IVA, with by far highest concentrations in the GI-tract, followed by the adrenal gland and the liver. In general, for both D-IVA and IVA, tissue:blood ratios appeared to be higher in SD rats than in LE rats, indicating increased distribution outside of the circulation. In SD rats concentrations in eye and skin were very low (BLQ in most samples), in LE rats the eye uveal tract:blood ratio was ~4 and skin was ~2.7 for non-pigmented skin and ~3 for pigmented skin for D-IVA. For IVA the values were similar with a ratio of ~2.3 for non-pigmented and pigmented skin/blood and 2.57 for eye uveal tract/blood.

A previous study with unlabeled TEZ showed distribution of TEZ to the lungs of SD rats, up to at least 144 hours post-dose, with lung/plasma ratios of 1.41 at 144 hrs to maximum 3.08 at the 2h time point.

**Metabolism**

Vanzacaftor is extensively metabolised via CYP metabolism in both rats and humans. However, no major metabolites were observed. Most metabolites are recovered from bile and very limited metabolites are present in plasma. In rats the most abundant radioactivity peak in plasma was VNZ, accounting for 94.7% of the AUC of total plasma radioactivity. M19 accounted for 5.3% of total plasma radioactivity. In humans the most abundant radioactivity peak in plasma was VNZ, accounting for 96.2% of the AUC of total plasma radioactivity. The most abundant metabolite, M19 (aminopyridine oxidation), accounted for 3.8% of the total circulating radioactivity.

D-IVA is metabolised mainly into M1-D-IVA and M6-D-IVA. In rat plasma, the most abundant radioactivity peak was D-IVA. M1-D-IVA and a metabolite of uncharacterised structure were observed. These metabolites also were observed for IVA in the study. It is unclear what percentage of total radioactivity in plasma could be attributed to parent, M1 and M6 (for both D-IVA and IVA) over the duration of the study (expressed as relative abundance of metabolites $AUC_{0\text{-tlast}}$) in rats, since this was not reported. Data from the study, however, were reported as percentage abundance at certain time points in plasma. At the first two time points where plasma concentrations were measured (2h and 6h) , there appears to be mainly D-IVA (approx. 80%) and about 10% M1-D-IVA in plasma. At the last time point (24h) there is approx. 90% D-IVA and 6% M1-D-IVA. For IVA at all time points measured, the parent is approx. 65%, whereas M1-IVA was approx. 25%. Therefore, it at least appears that D-IVA is more metabolically stable than IVA in rats. A similar trend is seen for dogs, where M1:parent ratios were 9.2% for ivacaftor and 4.2% for D-ivacaftor, indicating also an ~2 fold difference. In humans D-IVA is abundant in plasma 51.97% versus 26.94% for IVA, 35.01% versus 50.21% for M1-metabolites and 9.52% versus 19.26% for the M6-metabolites, indicating a similar trend as compared to non-clinical animal species. This furthermore indicates that M6-D-IVA is not a major metabolite in humans, while M6-IVA is a major metabolite.

*In vivo* metabolism of tezacaftor was investigated in $^{14}C$-radiolabel studies in rats and dogs. In rats, main metabolism involved the formation of a dehydrogenation metabolite (M1-TEZ), a phosphate conjugate of M1-TEZ (M5-TEZ), and an oxidation metabolite of M1-TEZ (M2-TEZ). In plasma of rats, primarily unchanged

tezacaftor, M1-TEZ (AUCinf 1.29-fold of tezacaftor) and M5-TEZ (AUCinf 0.75-fold of tezacaftor) were found. M2-TEZ was a major component in bile (approximately 25% of dose) but was low in plasma (0.05-fold of TEZ).

In dogs, metabolism mainly involved the formation of glucuronides of tezacaftor and M1-TEZ. In plasma, primarily unchanged tezacaftor, M3-TEZ (glucuronide of tezacaftor) and M12-TEZ (glucuronide of M1-TEZ) were found. M1-TEZ, M2-TEZ and M5-TEZ were low in dog plasma (<10% of total AUC). In bile, most of the radioactivity was associated with M3-TEZ and M11-TEZ (glucuronides of TEZ), and M12-TEZ and M13-TEZ (glucuronides of M1-TEZ).

Of the major circulating human metabolites (M1-TEZ, M2-TEZ and M5-TEZ), M1-TEZ and M5-TEZ were formed in significant amounts in rats but only to a low extent in dogs. M2-TEZ was not formed to a significant amount in rats and dogs.

**Excretion**

Vanzacaftor is excreted mainly in feces in humans and rats. Urinary excretion accounts for <1% in both rats and humans. In bile duct cannulated rats it was demonstrated that the main route of elimination is through bile (~50% of the dose). Excretion of unchanged compound was low (6.6% after IV administration).

Following a single oral administration of $^{14}$C-D-IVA to male rats, the mean total radioactivity recovery in bile and feces samples was 8.77% and 80.15%, respectively, over the 48-hour study. About 9% of the radioactivity was recovered from the carcass, indicating at 48 hours there is still a substantial amount left in tissues and probably the GI-tract (see Distribution section). Only a mean of 0.21% of the dose was recovered in urine. It appears in rats ~36% was D-IVA (compared to ~22% of the dose in feces being IVA in a $^{14}$C-IVA study). The rest is excreted as metabolites. Human D-IVA data is not available. IVA is excreted mainly via the feces in humans.

In intact rats, intact dogs and humans the main route of excretion of tezacaftor was via the faeces (75% - 79%, 58% and 72% of dose, respectively). Faecal excretion in intact dogs was relatively low probably due to liquid faeces in some of the animals as also a high amount in the cage rinse (18%) was found. Studies with bile duct cannulated (BDC) rats and dogs showed that large part of faecal excretion was due to excretion via the bile (53% and 50% of dose in orally dosed BDC rats and dogs respectively). Excretion via the urine was low, generally below 10% of dose in rats and dogs and 14% in humans. In rats, total radioactivity in faeces was excreted primarily as unchanged tezacaftor and M2-TEZ and in bile primarily as M2-TEZ. In dogs, radioactivity in bile was excreted primarily as glucuronides of tezacaftor and of M1-TEZ.

Tezacaftor, ivacaftor (D-IVA not studied) and vanzacaftor were all excreted in milk of lactating rats. For tezacaftor and ivacaftor the $C_{max}$ in milk was ~1.5 times the $C_{max}$ in maternal plasma. For vanzacaftor the $C_{max}$ in milk was 0.22 times the $C_{max}$ in plasma.

## 2.4.4. Toxicology

### *2.4.4.1. Single dose toxicity*

Single-dose toxicity studies were not conducted with VNZ or D-IVA since they are no longer recommended in the ICH M3 (R2) guidelines.

MTD was established at 2000 mg/kg in a micronucleus assay in female rats for VNZ. Similarly for TEZ, the MTD was established in the single dose micronucleus study in male mice to be >2000 mg/kg/day (for registration of Symkevi). The single-dose or acute oral toxicity profile of IVA was previously established (for registration of Kalydeco), the MTD in mice and rats was established at 2000 and 500 mg/kg, respectively.

The acute oral toxicity of tested compounds was considered to be of low order.

### *2.4.4.2. Repeat dose toxicity*

The repeat dose toxicology section focuses on VNZ, and is supplemented with known information on TEZ and IVA. Additionally, there is a bridging study for D-IVA (to IVA) and a combination toxicity study for the triple combination (VNZ+TEZ+D-IVA).

The GLP-compliant definitive repeat dose VNZ single agent studies were carried out for durations up to 28-days in mouse, 6 months in rat and 9 months in dog.

The repeat dose toxicology profile of TEZ and IVA were previously established in the support of the registration of Symkevi (EMA/CHMP/567306/2018) and Kalydeco (EMA/473279/2012), respectively, using a similar set of preclinical studies to that of VNZ in rat and dog. Pivotal studies for TEZ and IVA included a 6-month rat study and a 12-month dog study with each single agent component.

A bridge between the toxicity profiles of D-IVA and IVA has been established based on a GLP-compliant, 13-week single-agent repeat-dose toxicity study evaluating D-IVA in rats, which included an IVA comparator arm (100 mg/kg/day). Besides, 28 day rat and dog studies were also performed for D-IVA.

GLP-compliant combination toxicity studies (VNZ/TEZ/D-IVA) were carried out for the duration of 13 weeks in rat.

**Repeat dose toxicity in VNZ**

**VNZ in Mice**

A combined acute and subacute toxicity study in CByB6F1-Tg (HRAS)2Jic [RasH2] Wild Type Transgenic mice (phase I: 5 days and phase II: 28 days, respectively) was conducted with VNZ.

In Phase I, once daily gavage administration of VNZ to mice after 5 days was tolerated up to 100 mg/kg/day in both sexes. Mortality with associated clinical observations, body weight/food consumption effects, and clinical chemistry changes (indicative of hepatic effect) were noted at > 300 mg/kg/day. Therefore, the maximum tolerated dose (MTD) was 100 mg/kg/day, with AUC value 799 µg·h/ mL, represents 42-fold exposure multiple.

In Phase II, once daily gavage administration of VNZ at 0, 10, 30, and 100 mg/kg/day to mice after 28 days of dosing was tolerated up to 30 mg/kg/day in both sexes. VNZ-related mortality was found at 100 mg/kg/day as well as hepatic effects including higher mean ALT, glutamate dehydrogenase (GLDH), alkaline phosphatase (ALP) activity, and TBIL concentration, increased group mean liver weights and vacuolation. Therefore, NOAEL was 30 mg/kg/day, with AUC value 162 µg·h/ mL, represents 8.5-fold clinical exposure multiples.

This dose range-finding study in transgenic mice for 28 days indicated that high dose 100 mg/kg/day was not tolerated (EM 42). The liver findings aligned with rat studies in identifying the liver as a target organ, which is relevant since liver effects were observed in clinical trials and were included in the SmPC and RMP.

Consequently, 30 mg/kg/day was the NOAEL (EM 8.5) and was used in the 6-month carcinogenicity study in mice.

**VNZ in rats (7day, 28day, 6month)**

Clear gender exposure differences were identified in rats. Male rats have approximately half the exposure as female rats based on AUC with the same nominal administered dose. Therefore, in the pivotal 4-week and 26-week study, female animals received approximately half the dose that males did. This phenomena did not happen in clinical studies.

In the 28-days rat study VNZ was well tolerated with no adverse findings up to the highest dose evaluated. The NOAEL was determined to be 20 mg/kg/day for males and 10 mg/kg/day for females and represents 22- and 34-fold clinical exposure multiples.

In the pivotal long term (26 w + 6w recovery) repeat dose toxicity study, males were dosed 0, 5, 12, 25, 125 mg/kg/day; females were dosed 0, 2.5, 6, 12.5, 30 mg/kg/day.

Males did not tolerate VNZ at 125 mg/kg/day and they were terminated after 2 weeks of dosing due to VNZ-related mortalities and clinical signs indicative of declining clinical condition, body weight loss, and food consumption decrements. For most animals, erosions or ulcers of the non-glandular or glandular stomach related inflammatory response (higher total leukocyte, neutrophil and lymphocyte counts, higher fibrinogen concentrations) can be the cause of death.

Two main study females (30 mg/kg/day) were either euthanised early or found dead due to clinical observations indicative of declining clinical condition and body weight loss. The cause of death for one female was dilated kidneys noted macroscopically correlated with pyelonephritis and papillary necrosis and ulcers in the glandular stomach. The cause of death for the other female is black focus/foci noted on the glandular stomach and correlated with erosions in the glandular stomach. Two TK females were either found dead (Day 98) or euthanised early (Day 136), but no cause of death was determined for these TK animals.

Adverse effects were noted in males at 25 mg/kg/day and females at 30 mg/kg/day including lower body weight gain, liver and stomach effects. The identified target organs were liver and stomach.

For the liver, higher ALP and ALT activities and mean TBIL concentration (but lacked clear microscopic correlates in the liver for most animals), centrilobular vacuolar degeneration (2 males), higher creatine kinase (CK) activity (4 males) were found in males (=125 mg/kg). Hepatocellular vacuolar degeneration (minimal to mild) present primarily in centrilobular liver regions was found in males (≥ 12 mg/kg/day). Following the recovery period, hepatocellular vacuolar degeneration was present in 2 of 5 males at 25 mg/kg/day. Higher ALP and TBIL was found in surviving females at ≥12.5 mg/kg/day (recovery), mild multifocal hepatocellular necrosis were found in females (=30 mg/kg/day).

For the stomach, erosions or ulcers involving the non-glandular or glandular stomach correlated with hyperplasia/hyperkeratosis of the non-glandular stomach were found in males (=125mg/kg). In the glandular stomach, brown/black focus/foci in two females at 30 mg/kg/day correlated with minimal or mild erosions in the glandular mucosa (7 of 15 females affected) and/or severe ulceration of the glandular mucosa. One female at 30 mg/kg/day had mild epithelial hyperplasia and hyperkeratosis of the nonglandular gastric mucosa. These findings were not present following the recovery interval but were considered adverse, as these findings were related to the cause of death in several animals in the group that was terminated early (males at 125 mg/kg/day) and in the VNZ-related main study deaths in females at 30 mg/kg/day.

The observed liver and stomach effects at various doses included hepatocellular vacuolar degeneration, increased liver enzyme activities, and severe gastric erosions/ulcers, indicating hepatobiliary, hepatocellular, and gastric mucosal toxicity. The applicant did not discuss the clinical relevance of these findings.

For the stomach, the toxicity occurred at a high exposure margin (>59×). Additionally, similar findings were not observed in dog studies with high exposure margins (17×), and no such findings have been reported in humans. It has been noted that in rats, the highest distribution of 14C-VNZ-derived radioactivity was measured in the endocrine and metabolic/excretory systems, as well as the gastrointestinal (GI) tract. Given the physiological differences between rat and human stomachs, the relevance of found stomach toxicity in rat to humans is likely low. Hepatotoxicity is mentioned in the RMP as an important identified risk.

The findings in the lower dose group were all reversible. The NOAELs for VNZ 6-month rat study were 12 mg/kg/day in males and 12.5 mg/kg/day in females. At the NOAELs EMs were 21× in males and 59× in females.

**VNZ in dogs**

No toxicity was observed in the 14-day, 28-day, and 9-month toxicity studies in dogs. The NOAEL for administration for 9 months in dog is 10 mg/kg/day, the highest dose tested. This represents an exposure multiple of 103-fold over the intended clinical exposure. The highest does tested were 4 mg/kg/day in the 14 day study and 28 day study, resulting exposure multiple of 31 and 17 for females and 32 and 20 for males, respectively.

**Repeat dose toxicity studies with tezacaftor**

Safety data of tezacaftor has been previously assessed and is summarised here:

In repeat-dose toxicity studies previously conducted in support of the registration of Symkevi, lethality was noted in rats following sub-acute administration of tezacaftor at doses clearly exceeding the MTD in rats as evidenced by clinical signs of decreased food consumption and faecal volume, piloerection, and a thin appearance. Microscopic pathology findings in sub-acute toxicity studies in rats included macroscopic discoloration of the mucosa of the glandular stomach that correlated with minimal to mild focal erosion microscopically as well as mild to moderate thymic and minimal to mild splenic lymphoid depletion. Tezacaftor administration in rats up to 6 months (chronic) in duration were associated with body weight decrements, especially in the first few weeks of dosing but no tezacaftor-related target organ effects were identified at non-lethal dose levels. Repeat-dose toxicity studies in dogs up to 12 months (chronic) in duration failed to identify any target organs of tezacaftor-related toxicity at dose levels up to and exceeding the sub-chronic MTDs established in this species. A noteworthy and non-adverse finding observed in both rats and dogs following repeated administration was the microscopic finding of minimal to mild dilated lacteals in the villi tips of the duodenum, jejunum, and/or ileum. Dilatation of lacteals was considered non-adverse in all toxicity studies based on a lack of progression over time, severity of the finding, and the absence of tezacaftor-related clinical signs and/or clinical pathology findings.

**Repeat dose toxicity studies with ivacaftor**

Safety data of ivacaftor has been previously assessed and is summarised here:

Repeat-dose toxicity studies previously conducted in support of the registration of Kalydeco and ranging from sub-acute to chronic in duration identified the liver (mice and rats) as the only ivacaftor-related target organ of toxicity. The mechanism of hepatotoxicity is believed to be a rodent-specific phenomenon (xenobiotic overload of the liver attributed to hepatic accumulation of ivacaftor) and not relevant to humans. All other

noteworthy findings in rats (cardiomyopathy and tubular basophilia of kidneys) were either considered non-adverse or were ivacaftor-related exacerbations of commonly observed spontaneous degenerative lesions in aging rats, and are considered species-specific and not indicative of a human health risk.

Noteworthy findings in dogs were limited to cardiovascular findings of occasional instances of atrioventricular (AV) block and a slight increase in incidence of supraventricular premature complex (SVPC) runs noted following repeated administration. AV block is a well-documented background finding in this species which may be related to ivacaftor's demonstrated inhibition of the CaV1.2 (IC50 = 1.3 μM) channel. The SVPC runs were not accompanied by morphological changes in the heart or changes in health status and are believed to be due to exaggerated respiratory sinus arrhythmia, which is related to canine-specific control of heart rates and therefore would not translate to morbidity or mortality, in either dogs or humans.

**Repeat dose toxicity studies with D-IVA**

Repeat dose toxicity studies with D-IVA included 28-day studies in rats and dogs. In addition, a 3-month study was conducted in rats which included a comparator group that was administered IVA.

**D-IVA in rats**

Once daily oral administration of D-IVA (0, 50, 100, 200, and 400 mg/kg/day) for 28 days (+28d recovery) was well tolerated in rats at levels of 50 and 100 mg/kg/day. 28 days after cessation of dose administration, all changes were recovered compared to the vehicle control, except microscopic findings in the lung (lung alveolar histiocytosis, alveolar hyperplasia, and alveolar crystals, partial recovery, ≥ 100 mg/kg/d). Mortality was observed at 200 and 400 mg/kg/day resulting in early termination of the 400 mg/kg/day group on Day 15/16. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 100 mg/kg/day in rats. This represents an exposure multiple of 18-fold over the intended clinical exposure for males, and 31 fold for females.

A 13-week repeat-dose toxicity study with a 4-week recovery phase was conducted in rats. This study evaluated D-IVA at doses of 0, 8.75, 17.5, 35, or 100 mg/kg/day and included an IVA comparator arm (100 mg/kg/day). Toxicokinetics of the test article, D-IVA, comparator molecule ivacafator, and their associated metabolites were assessed. Sex differences in D-IVA and IVA Cmax and AUC0-24 values were observed but were less than 2-fold, with females generally higher than males. Mortality was observed in animals administered 100 mg/kg/day of either D-IVA (Main: 5/15 males; TK: 2/9 males and 2/9 females) or IVA (Main: 2/10 males; TK: 2/9 males). The only findings in these animals were clear oral discharge and/or thinning of the hair coat on the front feet, without preceding signs of morbidity.

Animals administered 100 mg/kg/day D-IVA or IVA underwent an early terminal sacrifice on Day 86 of the dosing phase due to mortality in these groups. Except article related clinical observations included clear oral discharge, alopecia , thinning haircoat and sensitivity to touch (partial reversible) and increased thyroid/parathyroid weights (no microscopic correlates), all other findings were reversible after 4 weeks recovery. Similar findings with lower magnitude were seen in animals in the (8.75, 17.5, 35 D-IVA) group that survived to their scheduled sacrifice. The NOAEL for D-IVA in this study was 35 mg/kg/day. This represents an exposure multiple of 10-fold over the intended clinical exposure for males, and 14 fold for females. Overall findings in this 13-week toxicity study for D-IVA and IVA were similar (at 100 mg/kg/day to rats) and suggested a comparable toxicity profile.

**D-IVA in dogs**

A 28-day+ 4 week recovery repeat-dose toxicity study was conducted with D-IVA in Beagle Dogs via oral gavage at 0, 7.5, 12.5, 20, and 60 mg/kg/day.

D-IVA was well tolerated up to 60 mg/kg/day based on clinical observations, body weights, clinical pathology, and histopathology for the main study animals. D-IVA-related clinical observations included a dose-related increase in soft/liquid/mucoid feces and emesis at ≥ 20 mg/kg/day during the dosing phase. Only soft stools was observed during the recovery period generally remaining through Day 30 (except the 60 mg/kg/day females which generally remained through Day 50). Besides, evaluation of electrocardiology morphology indicated prolonged PR interval at 60 mg/kg/day in males and females during the last week of dose administration (Day 26). This finding was no longer present during the recovery phase (Day 53/54). Based on these results, the no-observed-adverse-effect level (NOAEL) for D-IVA was considered to be 20 mg/kg/day. This represents an exposure multiple of 18-fold over the intended clinical exposure for males, and 14 fold for females.

**Combination studies with VNZ+TEZ+D-IVA**

**Combination studies in rats**

The 13 weeks toxicity study in rats was conducted to evaluate the mono toxicity (VNZ/D-IVA/TEZ alone 2.5/17.5/45 mg/kg/day), or dual toxicity (VNZ+D-IVA 2.5+17.5mg/kg/day), or triple toxicity (VNZ+D-IVA+TEZ 2.5+17.5+45 mg/kg/day). Articles were administered once daily via oral gavage, only one dose level for each component was selected (VNZ 2.5, D-IVA 17.5, TZE 45).

In summary, all stand alone and combination (VNZ/D-IVA and VNZ/TEZ/D-IVA) treatments were well tolerated at the tested dose. Effects found such as transient decreased body weight or food consumption, increased mean urine volume and mean urine pH, decreased urine specific gravity, decreased mean triglyceride concentrations, increased AST, ALT, GLDH activities were at small magnitude and lack of other correlative findings, therefore they were not considered adverse. These findings were also observed in previously conducted monotherapy studies. There were no new target organs noted or additive effects when VNZ was administered in dual or triple combination. TK study showed that AUC0-24hr values to VNZ and TEZ were generally lower when administered alone compared to triple combination group. It is the other way round for D-IVA. The exposure when administered as triple combination was sufficient. Only one dose was tested for the triple combination: 2.5+17.5+45 mg/kg/day (VNZ+D-IVA+TEZ), and with this dose, no toxic effects were noted. The AUC values on day 91 were 75.4/82.7/105 µg•h/mL for males and 164/56/243 µg•h/mL for females. The EMs at this dose were 4/2.1/1.2× for males and 8.6/1.4/2.7× for females.

### *2.4.4.3. Genotoxicity*

VNZ and D-IVA were not genotoxic in *in vitro* Ames test, or micronucleus assay in human TK6 lymphoblastoid cells in presence or absence of S9 metabolizing mix. VNZ and D-IVA were also not genotoxic in in vivo micronucleus test in SD rats. Similarly, ivacaftor and tezacaftor are not genotoxic, as has been previously established.

### *2.4.4.4. Carcinogenicity*

The designs of carcinogenicity studies for VNZ, TEZ and IVA are in line with recommendations set forth in the ICH S1A, ICH S1B and ICH S1C (R2) guidelines.

In the case of VNZ, the studies consisted of a 6-month Tg.rasH2 transgenic mouse carcinogenicity study and a 2-year rat carcinogenicity study. VNZ did not demonstrate a carcinogenic potential at the doses evaluated in the Tg.rasH2 mouse up to 30mg/kg/day. A 2-year carcinogenicity study was conducted in Sprague-Dawley

rats, with five groups (150 or 75 animals per group) receiving vehicle/control or test article at doses of 0, 1, 3, 7.5 mg/kg/day (females), or 12 mg/kg/day (males) once daily for up to 98 weeks. TK groups were included. Increased incidences of mammary gland tumours, islet cell adenomas, acinar adenomas, uterine granular cell tumours, and C-cell adenomas were observed; however, these findings were within historical control data and lacked dose-response relationships. Although pancreatic acinar adenomas (12 mg/kg/day, males), skin haemangiosarcomas, and malignant lymphomas (1 mg/kg/day, females) showed statistical significance in certain tests, no dose-response relationship or supporting evidence was identified. The historical control data are provided as a reference article which cannot be found in the public domain, however, since the supporting evidence is sufficient, these findings were therefore considered incidental and not VX-121-related.

The only VX-121-related non-neoplastic microscopic finding was minimal to moderate centrilobular vacuolation in the liver. The Day 358 (Week 52) Cmax and AUC0-24hr values at 12 mg/kg/day were 55.6 µg/mL and 954 hrµg/mL in males, and at 7.5 mg/kg/day were 49.8 µg/mL and 987 hrµg/mL in females. The high dose was selected to provide an anticipated 28x multiple of the clinical exposure of 14.2 µg·h/mL at the Phase 3 clinical dose of 20 mg/day. Compared to male rats at 12 mg/kg/day the exposure margin is 67x and for female rats at 7.5 mg/kg/day the exposure margin is 69.5x. In conclusion, VX-121 was not carcinogenic in the 2-year rat carcinogenicity study.

The carcinogenic potential of TEZ was previously assessed for registration of Symkevi, with a 6-month transgenic mouse carcinogenicity study conducted in Tg.rasH2 mice and a 2-year rat carcinogenicity study, while the carcinogenic potential of IVA had previously been assessed for the registration of Kalydeco in pivotal lifetime (2-year) rodent carcinogenicity bioassays conducted in mice and rats. Systemic exposures to TEZ and IVA and primary metabolites (M1-TEZ, M2-TEZ and M1-IVA and M6-IVA) were demonstrated in TK evaluations included in the design of both the mouse and rat studies and both TEZ and IVA were found to be non-carcinogenic in these assessments.

No carcinogenicity studies were performed with D-IVA. This can be agreed.

Combination carcinogenicity studies involving the co-administration of VNZ, TEZ, and D-IVA were not performed. It can be agreed that studies conducted on each individual entity can be considered adequate to assess the carcinogenic risk associated with co-administration. However, since the 2-year rat study for VNZ is not yet completed, the carcinogenicity potential cannot be determined at the moment for the VNZ, TEZ, and D-IVA co-administration.

#### *2.4.4.5. Reproductive and developmental toxicity*

Developmental and reproductive toxicity studies with VNZ included EFD, FEED and PPND studies.

The reproductive and developmental toxicity profiles of TEZ and IVA were previously established in a similar set of studies conducted in rats and rabbits in support of the registration of Symkevi and Kalydeco.

No reproductive toxicity studies have been conducted with D-IVA. A bridge between the toxicity profiles of D-IVA and IVA has been adequately established in the 13-week rat toxicity study. Data from the IVA reproductive toxicity studies support the development of D-IVA.

Combination reproductive and developmental toxicity studies involving the co-administration of VNZ, TEZ, and D-IVA were not performed as the studies conducted on each individual entity were considered adequate to assess the risk associated with co-administration and provided no evidence for potential additive or synergistic interaction.

**Reproductive and developmental toxicity for VNZ**

Development and reproductive toxicity studies with VNZ included EFD, FEED, and PPND studies.

VNZ had no effects in the rats FEED study at tested doses. The NOEL for males and females for systemic and reproductive toxicity were the highest doses studied (12.5 mg/kg/day for males and 10 mg/kg/day for females). The Day 56 AUC0-24h at the NOEL of 12.5 mg/kg/day for males was 361 µg·h/mL and provided an EM of 19× over the anticipated therapeutic exposure. The female exposure values were not assessed but are inferred from the rat EFD study which included the same dose levels.

In the pivotal EFD toxicity studies in rats, VNZ did not cause maternal or embryo/fetal developmental toxicity up to the highest dose evaluated. The NOEL for maternal or embryo/fetal developmental toxicity was 10 mg/kg/day; the mean AUC0-24h on Gestation Day (GD) 17 was 565 µg·h/mL and provided an EM of 30×.

In the pivotal EFD toxicity studies in rabbits, VNZ was maternally toxic at the high dose (70 mg/kg/day, AUC0-24h on GD 20 was 1350 µg·h/mL, EM of 71×). Three females were euthanised earlier. Surviving females in this group were noted with VNZ related clinical findings of reduced fecal size and output, body weight losses or lower mean body weight gains and lower mean food consumption, lower Mean gravid uterine weight. A higher mean litter proportion of post-implantation loss with a corresponding lower mean number of live fetuses was noted in this group. Fetal effects at this dose included a malformation of the kidney (malpositioned or fused) and a skeletal variation (supernumerary thoracolumbar full ribs). The intermediate dose (40 mg/kg/day) was the NOAEL for maternal or embryo/fetal developmental toxicity. The mean AUC0-24h on GD 20 was 410 µg·h/mL and provided an EM of 22×.

VNZ had no effects in the PPND study in rats, no VNZ related maternal (F0) or pup (F1) effects were noted up to the highest dose tested (10 mg/kg/day). The NOEL was 10 mg/kg/day, the maternal AUC0-24h was 339 µg·h/mL, and the EM was 18×.

**Reproductive and Developmental Toxicity for TEZ and IVA**

For TEZ, the overall conclusions from reproductive and developmental toxicity studies indicate that it is not a reproductive and/or developmental toxicant. TEZ did not result in toxicity to male or female reproductive systems or have effects on early embryonic development. Effects on fetal development and growth of offspring (lower F1 generation survival/lactation indices, decreased pup body weights pre- and post-weaning and lower reproductive capacity in F1 generation rats) were only noted at significantly maternally toxic dose levels.

The overall conclusions from reproductive and developmental toxicity studies evaluating IVA indicate that it had only minimal effects on female reproduction and fetal development in rats attributable to significant maternal toxicity.

**Juvenile study VNZ**

Juvenile male and female SD rats were administered VNZ once daily from PND 7 through 70. Male dose levels were 0, 2.5, 10, and 25 mg/kg/day and female dose levels were 0, 2.5, 6, and 12.5 mg/kg/day.

Non-adverse lower mean body weights, body weight gains, and food consumption were noted at 25 mg/kg/day in males. Non-adverse haematology findings (↑LYMPH, WBC) were noted in males above 10 mg/kg/day. Higher incidence of unilateral renal pelvic dilatation was found in a few animals but was considered congenital and not VNZ-related. Clinical chemistry findings were observed including increased TBIL (M= 25; F ≥ 2.5), TBA (M= 25 ; F= 12.5 ), GGT (M &F ≥ 2.5) as well as decreased CHOL (M= 25, F=12.5), UREA (F= 12.5) and increased PHOS (M= 25).

**Juvenile study TEZ and IVA**

Juvenile toxicity studies with TEZ in rats exposed during postnatal day (PND) 7 to 35 showed mortality and moribundity even at low doses. In particular, some animals dosed with TEZ prior to PND 14 experienced convulsions and/or died. Findings were dose related and generally more severe when dosing with TEZ was initiated earlier in the postnatal period. Exposure in rats from PND 21 to 49 did not show toxicity at the highest dose which was approximately 1.2× the intended human exposure. These findings are not relevant for the current application where the intended paediatric population are above 6 year old.
TEZ and its metabolite, M1-TEZ, are substrates for P-gp. Lower brain levels of P-gp activity in younger rats resulted in higher brain levels of TEZ and M1-TEZ. These findings are not relevant for the paediatric population 1 year of age and older, for whom levels of P-gp activity are equivalent to levels observed in adults.
Juvenile toxicity studies conducted with IVA identified the eye (lens opacities/cataracts) as a target organ of toxicity. Findings of cataracts were observed in juvenile rats dosed from PND 7 through 35 with IVA dose levels of 10 mg/kg/day and higher. No other target organ toxicities were identified, particularly in developing organ systems, in the juvenile rat toxicity study. Cataracts were not detected in repeat-dose toxicity studies conducted in older mice, rats, or dogs, including chronic toxicity studies using rats as young as 7 weeks old at dosing initiation and dogs as young as 3.5 months old at dosing initiation. Following identification of the eye as a target organ of toxicity in juvenile rats, a retrospective evaluation revealed there was no morphological evidence of cataracts or lenticular degeneration in fetal eyes examined from the rat EFD study with IVA. Cataracts were also not detected in rat pups exposed to IVA to a certain extent through milk ingestion up to PND 20.

### *2.4.4.6. Toxicokinetic data*

Toxicokinetic data and assessment are presented in the Pharmacokinetics Absorption section 3.2 of the non-clinical AR.

Overall, it appears that VNZ, D-IVA and TEZ have similar kinetic properties in the different non-clinical animal species. Within species exposure differences between males and females were observed in rats, but these are not considered clinically relevant. First of all, the differences were mostly <2-fold difference and secondly, they were not observed in non-rodents (e.g. dogs). At NOAEL levels, exposure multiples were more than sufficient in all non-clinical animal species for VNZ and D-IVA. TEZ was only assessed in combination studies with an exposure multiple of 1.2 for males and 2.7 for females at a dose where no toxicity was observed (only 1 dose tested). Since TEZ has been well studied and approved in a previous MAA, this limited amount of data is deemed acceptable.

Exposure multiples >1.0 were achieved at NOAEL for the major human metabolite M1-D-IVA in rats. In dogs the exposure multiple was 0.44 at NOAEL. For M6-D-IVA exposure in animals was lower, with exposure multiples of 0.17 in rats and 0.25 in dogs. However, in humans, metabolite M6-D-IVA accounted for 9.52% in plasma. Therefore, it is not considered a major metabolite.

In conclusion, the pre-clinical pharmacokinetic and toxicokinetic data appear to be sufficient to support the clinical use of VNZ/D-IVA/TEZ. Exposure margins at NOEAL are sufficiently high compared to human exposure at clinical doses.

### *2.4.4.7. Tolerance*

As part of a handler safety package, *in vitro* and in vivo GLP studies were conducted to assess VNZ irritation potential in dermal and ocular tissues. The findings indicated that VNZ is not a dermal irritant. A prediction for ocular irritation could not be made in the *in vitro* bovine corneal opacity and permeability test with VNZ. However, a follow up study in the Reconstructed Human Cornea-like Epithelium (RHCE) Model concluded that VNZ was not predicted to induce ocular irritation.

As part of the development and registration of Symkevi and Kalydeco, both tezacaftor and ivacaftor were assessed in similar package of handler safety studies (irritation potential in dermal and ocular tissues and the potential for skin sensitisation), which concluded both tezacaftor and ivacaftor to be a non-irritant and non-sensitizing in dermal studies and that tezacaftor was reported as a mild irritant in ocular irritancy, while IVA was not.

### *2.4.4.8. Other toxicity studies*

**Antigenicity**

The GLP-compliant murine local lymph node assay (LLNA) assay demonstrated that that VNZ, TEZ and IVA are negative for skin sensitizing potential.

**Metabolites**

There were no major human metabolites identified for VNZ.

Major human metabolites of TEZ (M2-TEZ, M1-TEZ and M5-TEZ) were evaluated and appropriately qualified in preclinical toxicity studies in support of the registration of Symkevi.

Major metabolites of IVA (M1-IVA and M6-IVA) were evaluated in support of the registration of Kalydeco.

Major metabolites of D-IVA (M1-D-IVA and M6-D-IVA) were quantified in preclinical toxicity studies conducted over 13 weeks in rats and 4 weeks in dogs. Independent toxicity evaluations of these metabolites were not conducted. The rationale for this approach is that M1-IVA and M6-IVA have been fully characterised in previous toxicity studies with IVA in rats and dogs. Furthermore, the systemic exposures of M1-D-IVA and M6-D-IVA were lower than those of their corresponding metabolites, M1-IVA and M6-IVA, in both species. It should be noted that for comparisons of metabolite levels in dogs, data from the D-IVA 28-day dog study were used alongside data from the IVA 12-month dog study.

**Studies on impurities**

No standalone experimental studies were conducted specifically to qualify impurities in VNZ. All specified impurities and degradation products in VNZ drug substance and drug product were qualified in the repeat-dose animal toxicity studies.

In the in-silico analysis study report VX-121-TX-030, the structure of VNZ, along with 43 intermediates and known or suspected impurities in its synthesis, was evaluated for potential DNA reactivity using two in silico software packages (DEREK and SARAH) in combination with expert analysis, following the guidelines outlined in ICH M7. For cases where DEREK and SARAH provided discordant predictions, 13 consensus predictions were obtained using an additional in silico tool, LSMA. The tested impurities were non mutagenic.

Specified impurities in the IVA and TEZ SDD were controlled to ICH classification limits or were qualified and/or justified previously for the registration of Kalydeco and Symkevi.

No impurity studies were conducted for D-IVA. D-IVA was synthesised using the same process method as IVA, and this can be agreed.

**Phototoxicity studies**

An initial assessment of phototoxic potential of VNZ indicates that the molecule absorbs in the UV-visible spectrum 206 to 347 nm. A GLP 3-day multi-dose phototoxicity study in pigmented rats was conducted, and there was no evidence of cutaneous or ocular phototoxicity after a 3-day oral (gavage) administration of VNZ at doses as high as 10 mg/kg/day, followed by a single exposure to UVR approximately 8 hours post-dose.

Tezacaftor did not demonstrate phototoxic potential in this assay and therefore does not appear to present any risk of phototoxicity in humans. Ivacaftor was not tested for phototoxicity.

## 2.4.5. Ecotoxicity/environmental risk assessment

**Table 5 Vanzacaftor**

| **Substance** (INN/Invented Name): VX-121/Vanzacaftor | | | |
|---|---|---|---|
| **CAS-number** (if available): 2374124-50-0 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD 123 | pH 5, log $D_{ow}$ = 7.4<br>pH 7, log $D_{ow}$ = 3.6<br>pH 9, log $D_{ow}$ = 4.0<br><br>log $K_{ow}$ determined from log $D_{ow}$ at pH 5 and p$K_a$ of 4.6 = 7.95 | Potential PBT: Y |
| ***Phase I*** | | | |
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| $PEC_{sw}$, default | 0.1 | µg/L | ≥ 0.01 threshold: Y |
| Other concerns (e.g. chemical class) | | | N |

Vanzacaftor(VX-121) is potentially a PBT substance.

Considering the above data and the environmental risk assessment, it cannot be concluded if VX-121 is expected to pose a risk to the surface water and groundwater compartment and the sewage treatment plant. In absence of the full documentation underpinning the Fpen refinement and alinement of the Fpen between the three ingredients, a Phase II assessment is warranted (see Discussion on non-clinical aspects).

**Table 6 Tezacaftor**

| **Substance (INN/Invented Name):** tezacaftor | | | |
|---|---|---|---|
| **CAS-number (if available):** 1152311-62-0 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | log $K_{ow}$ 3.58 | Potential PBT (N) |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | 3.58 | not B |
| | BCF | 7.7 L/kg | not B |

| **PBT-statement :** | Tezacaftor (VX-661) is considered not PBT nor vPvB | | | | |
|---|---|---|---|---|---|
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Conclusion** |
| $PEC_{surface\ water}$, refined $F_{pen}$ | $1.25x10^{-2}$ | µg/L | | | > 0.01 threshold (Y) |
| Other concerns (e.g. chemical class) | not investigated | not listed in ECHAs CL Inventory | | | |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 106 | 733 L/kg (domestic sludge)<br>879 L/kg (domestic sludge)<br>957 L/kg (sandy loam)<br>920 L/kg (sandy loam)<br>1116 L/kg (clay) | | | Geometric mean for sludge:<br>851 L/kg<br>Geometric mean for soil:<br>994 L/kg |
| Ready Biodegradability Test | OECD 301 | not available | | | not required |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50,\ water}$ = 26.9/16.5 d (l/l)<br>$DT_{50,\ system}$ = 58.1/22.3 d (l/l)<br><br>% shifting to sediment 16-20% at d 14, increasing thereafter | | | l=lake<br>$DT_{50}$ values at 20°C. |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*P. subcapitata* | OECD 201 | NOEC | 0.91 | mg/L | growth rate |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | 1.2 | mg/L | growth |
| Fish, Early Life Stage Toxicity Test/*P. Promelas* | OECD 210 | NOEC | 1.2 | mg/L | body length |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | EC10 | >1000 | mg/L | respiration |
| ***Phase IIb Studies*** | | | | | |
| Bioaccumulation/*C. carpio* | OECD 305 | $BCF_{SS,\ L}$ | 7.7 | L/kg | |
| Sediment dwelling organism/*C. riparius* | OECD 281 | NOEC | 310 | $mg/kg_{dw}$ | normalised to 10% o.c. |

**Table 7 Deutivacaftor**

| **Substance (INN/Invented Name):** deutivacaftor* | | | |
|---|---|---|---|
| **CAS-number (if available):** 1413431-07-8 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | log $K_{ow}$ >4.7 | Potential PBT (Y) |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant for conclusion** | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | >4.7 | |
| | BCF | 39.2 L/kg | not B |
| Persistence | DegT50 | $DT_{50\ water}$ 3.6, 9.3 d (l/l)<br>$DT_{50\ system}$ 1233, 261 d (l/l)<br>$DT_{50\ soil}$ = 3213, 1201, 730, 1598 d | l=lake. $DT_{50}$ values corrected to 12°C.<br><br>Conclusion: vP |
| Toxicity | NOEC algae<br>NOEC crustacea | >0.0547 mg/L<br>0.0031 mg/L<br>≥0.029 mg/L | T |

| | | | | | |
|---|---|---|---|---|---|
| | NOEC fish | | | | |
| | CMR | Repr 2 (notified classification) | | | potentially T |
| **PBT-statement :** | VX-770 is considered not PBT nor vPvB | | | | |
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Conclusion** |
| $PEC_{surface\ water}$ refined $F_{pen}$ This is a summed $PEC_{sw}$ for 4 products containing ivacaftor: Orkambi™, Kalydeco™, Symkevi™ and Kaftrio | 0.081 | µg/L | | | > 0.01 threshold (Y) |
| Other concerns (e.g. chemical class) | Repr 2 | notified classification | | | |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 106 | $K_{oc\ sludge}$ = 11800, 10800 L/kg<br>$K_{oc\ soil}$= 3710, 1970, 5900 L/kg | | | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50\ water}$ 1.7, 4.4 d (l/l)<br>$DT_{50\ system}$ 581, 123 d (l/l)<br>% shifting to sediment = 68-79% at d 14. | | | l=lake; $DT_{50}$ values at 20°C; Significant shifting to sediment observed. |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*P. subcapitata* | OECD 201 | NOEC | >54.7 | µg/L | growth rate |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | 3.1 | µg/L | reproduction |
| Fish, Early Life Stage Toxicity Test/*P. promelas* | OECD 210 | NOEC | ≥29 | µg/L | hatching, survival, growth |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | EC10 | >1000 | mg/L | respiration |
| ***Phase IIb Studies*** | | | | | |
| Bioaccumulation/*O. mykiss* | OECD 305 | $BCF_{KL}$ | 39.2 | L/kg | lipids: 5.5-7.6% |
| Aerobic and anaerobic transformation in soil | OECD 307 | DT50 | 1513, 566, 344, 753 | d | for all 4 soils |
| Soil Microorganisms: Nitrogen Transformation Test | OECD 216 | no effect | ≥1.81 | mg/kg | |
| Terrestrial Plants, Growth Test/*A. Cepa, A. sativa, B. oleracea, D. carota, L. sativa, L. esculentum* | OECD 208 | NOEC | ≥1818** | mg/kg | normalised to 2% o.c. |
| Earthworm, Acute Toxicity Tests/*E. fetida* | OECD 207 | NOEC | >417** | mg/kg | normalised to 2% o.c. |
| Collembola, Reproduction Test/*F. candida* | ISO 11267 | NOEC | ≥690** | mg/kg | normalised to 2% o.c. |
| Sediment dwelling organism/*C. riparius* | OECD 218 | NOEC | ≥7463 | mg/kg | normalised to 10% o.c. |

* *All endpoints presented are for ivacaftor, these are considered relevant for deutivacaftor*

## 2.4.6. Discussion on non-clinical aspects

**Pharmacology**

VNZ/TEZ/D-IVA is a triple combination (TC) regimen composed of three CFTR modulators: two CFTR correctors vanzacaftor(VNZ) and tezacaftor (TEZ), and a CFTR potentiator deutivacaftor (D-IVA). VNZ is a novel next-generation CFTR corrector. D-IVA is a deuterated isotopologue of IVA. This modification aims to alter the pharmacokinetic properties (e.g. increase half-life), thereby supporting a once daily dosing regimen (instead of twice daily with IVA). TEZ is also part of previously approved CFTR therapies Symkevi (IVA+TEZ) and Kaftrio (ELX+TEZ+IVA).

The pharmacology of VNZ alone and/or in combination with TEZ and/or D-IVA was characterised in a variety of biochemical and functional assays. These assays were also used for the registration of Kalydeco (IVA), Symkevi (IVA+TEZ) and Kaftrio (IVA+TEZ+ELX). As there is no validated animal model for CF that fully mimics the human multi organ affected disease, the use of *in vitro* systems to study the pharmacology can be accepted.

To demonstrate comparable pharmacodynamic properties of D-IVA to IVA, a direct comparison between IVA and D-IVA in CF-HBE cells with the *F508del/F508del* and *F508del*/MF genotype was conducted (Study Q142). This demonstrated similar potency and efficacy between IVA and D-IVA for this mutation. The applicant was invited to provide additional justification to substantiate the assumption that all IVA-responsive mutations are D-IVA responsive as well but indicated that there are no additional data. The applicant assumes that D-IVA will behave similarly to IVA in the FRT assay based since (I) they have the same binding site confirmed by cryoEM imaging, (II) same mechanism of action, and (III) same PD profile in the CF-HBE cells, (IV) similar efficacy in subjects with a gating mutation. Additionally, the applicant provided FRT results for mutations tested with TEZ/IVA and TEZ/D-IVA that were non-responsive in the FRT assay with ELX/TEZ/IVA but were responsive with VNZ/TEZ/D-IVA. Overall, these results demonstrate that $Cl^-$ transport values between TEZ/IVA and TEZ/D-IVA were largely similar to each other, consistent with the data summarised above. This justification is considered sufficient to conclude that IVA and D-IVA have comparable pharmacodynamic properties. Importantly, the applicant agreed with the CHMP to drop the request for a NAS status for D-IVA.

In addition, the applicant claims that VNZ works synergistically with TEZ and D-IVA to increase CFTR-mediated Cl- transport. This statement is not supported by CHMP.

The available data demonstrates that VNZ is a CFTR corrector and has overlapping binding sites with ELX (part of Kaftrio) but also has unique binding sites at the CFTR protein. TEZ+D-IVA+VNZ treatment results in increased processing and trafficking of the F508del-CFTR protein in CF-HBE cells with the *F508del/F508del* and *F508del*/MF genotype. This also resulted in improved $Cl^-$ transport in CF-HBE cells with the *F508del/F508del* and *F508del*/MF genotype. In addition, improved $Cl^-$ transport was also observed in CF-HBE cells with the *N1303K / N1303K* and *N1303K* /MF genotype.

The applicant is proposing a similar approach for the current indication of VNZ+TEZ+D-IVA as for the extension of indication for Kaftrio recently concluded (EMEA/H/C/005269/WS2551).

In Study P289, all 88 IVA-responsive non-*F508del* mutations were also responsive to the dual combination of TEZ+IVA. Likewise, all 148 mutations that responded to IVA and/or IVA+TEZ treatment, were also IVA+TEZ+ELX responsive. The applicant states that these 148 mutations are also expected to be responsive to VNZ+TEZ+D-IVA in the FRT assay, since TEZ and (D-)IVA are both components of the new triple combination with VNZ, and IVA responsive mutations are expected to be responsive to D-IVA as well. In the

FRT assay it is shown that of 475 mutations tested with VNZ/TEZ/D-IVA, 54 were not responsive to any CFTR modulator, 47 were responsive to VNZ/TEZ/D-IVA only, and the remaining 374 mutations were responsive to both VNZ/TEZ/D-IVA and ELX/TEZ/IVA. These data show that none of the tested mutations were responsive to ELX/TEZ/IVA only. The provided data and argumentation from the MAH do not exclude the possibility of mutations that are responsive to ELX/TEZ/IVA but not to VNZ/TEZ/D-IVA. However, should such very rare mutations exist, these would only concern a very small number of patients, considering that only ultra rare mutations have not yet been tested in the FRT assay.

Adequate cross study comparison between the studies conducted in CF-HBE cells and in the FRT assay is not possible, hampering a comparison of VNZ+D-IVA+TEZ vs. ELX+IVA+TEZ response. Therefore, the applicant's' statement that the triple combination with VNZ will provide greater improvement in CFTR-mediated Cl- transport than the triple combination with ELX, is not supported by CHMP from a non-clinical point of view since it cannot be adequately substantiated by the provided non-clinical data.

VNZ did not demonstrate any relevant findings in secondary pharmacodynamics and safety pharmacology studies, at concentrations well above clinical exposure. Secondary pharmacology studies and safety pharmacology studies for TEZ and IVA were submitted and assessed with the previous marketing authorisation procedures for Kalydeco and Symkevi. D-IVA and IVA demonstrated comparable results in a secondary PD screen, so no additional off-target effects are expected for D-IVA. Results suggested a low potential for VNZ, TEZ and D-IVA to elicit effects on CNS, respiratory, or cardiovascular parameter parameters at clinically relevant exposures.

**Pharmacokinetics**

Overall, it appears that VNZ, D-IVA and TEZ have similar pharmacokinetic properties in the different non-clinical animal species. All compounds were absorbed after oral administration. Some accumulation over time was observed for D-IVA and metabolites over time. Within species exposure differences between males and females were observed in rats, but these are not considered clinically relevant. First of all, the differences were mostly <2-fold or ~2-fold difference and secondly, they were not observed in non-rodents (e.g. dogs). Distribution was highest in the GI-tract, liver and kidneys for all three compounds in rats. No substantial binding to melanin-containing tissues was observed. Metabolism was comparable between animal species and humans. VNZ has no major metabolites in animal species and humans. D-IVA is more metabolically stable than IVA, with M1-D-IVA and M6-D-IVA as the main metabolites. These metabolites were also formed in humans. M1-D-IVA was a major metabolite and M6-D-IVA was not but is still present at 9.5% in human plasma. Excretion for all three compounds was as metabolites via feces in all animal species and humans. Urinary excretion was very limited for all compounds.

At NOAEL levels, exposure multiples were more than sufficient in all non-clinical animal species for VNZ and D-IVA. TEZ was only assessed in combination studies with an exposure multiple of 1.2 for males and 2.7 for females at a dose where no toxicity was observed (only 1 dose tested). Since TEZ has been well studied and approved in a previous MAA, this limited amount of data is deemed acceptable.

Exposure multiples >1.0 were achieved at NOAEL for the major human metabolite M1-D-IVA in rats. In dogs the exposure multiple was 0.44 at NOAEL. For M6-D-IVA exposure in animals was lower, with exposure multiples of 0.17 in rats and 0.25 in dogs. However, in humans, metabolite M6-D-IVA accounted for 9.52% in plasma. Therefore, it is not considered a major metabolite.

**Toxicology**

For the VNZ 26 week repeat dose toxicity study in rats, it has been noted that from the study report, males numbered 9001-9020 were assigned to group 9, receiving a dose of 125 mg/kg/day as main study animals (15/sex/group for main study and 5/s/group for recovery), and males numbered 18001-18010 were assigned for toxicokinetics (TK). For main study and recovery males, there were 4 found dead, 6 euthanised in extremis, and 10 early termination (Day 14). Moreover, 2 male toxicokinetic (TK) rats administered 125 mg/kg/day were euthanised in extremis. For the unscheduled deaths, the cause of death was undetermined for 6 males and associated with stomach erosions/ulcerations for 4 males. For the 30 mg/kg/day females, there were 1 found dead, 1 euthanised in extremis, and 18 scheduled terminations (including recovery rats). For the unscheduled deaths, the cause of death was associated with stomach erosions in 1 female and pyelonephritis in 1 female. The exposure multiple in the 30 mg/kg/day females was 136x the maximum recommended human dose (MRHD). No exposure values were available for the 125 mg/kg/day males, however, at the next lower dose (25 mg/kg/day) the exposure multiple was 42x the MRHD. These large exposure margins confirm that the findings at these poorly tolerated doses were not clinically relevant.

In the rat 13 weeks study for D-IVA, mortality was observed in animals administered 100 mg/kg/day of either D-IVA (Main: 5/15 males; TK: 2/9 males and 2/9 females) or IVA (Main: 2/15 males; TK: 2/9 males). The only findings in these animals were clear oral discharge and/or thinning of the hair coat on the front feet, without preceding signs of morbidity. However, in the previous 3-month rat study (Kalydeco registration report), hardly any effects were observed at 100 mg/kg/day of IVA. The applicant provides a plausible explanation for the unexplained deaths observed at 100 mg/kg/day in the 13-week rat study (CTP-656-TX-080) by attributing them to higher systemic exposures achieved in this study compared to the earlier 13-week study (VX-770-TX-001). In study VX-770-TX-001, 100 mg/kg/day was the no-observed-adverse-effect level (NOAEL) and the associated exposures (male/female) on Day 90 were **271.5/298.6** µg·h/mL. In this study, unscheduled deaths were observed at 200 and 400 mg/kg/day with the 400 mg/kg/day dose group being terminated on Day 31. Corresponding exposures were **565.3/677.5** µg·h/mL at 200 mg/kg/day and **405.8/823.7** µg·h/mL at 400 mg/kg/day (Day 28). In study CTP-656-TX-080, systemic exposure at 100 mg/kg/day on Day 85 were **496/747** µg·h/mL for D-IVA and **373/657** µg·h/mL for IVA. Therefore, the reason for the unexplained deaths in study CTP-656-TX-080 is that the exposures at 100 mg/kg/day in study CTP-656-TX-080 overlapped with the exposures associated with mortality at 200 and 400 mg/kg/day in study VX-770-TX-001. While the exact cause of the differences in systemic exposure between the two studies remains unclear, the applicant reasonably attributes them to differences in CROs, test article source, and bioavailability.

In the VNZ rat juvenile study, the applicant's justification that the liver was not a target organ in the juvenile toxicity study is supported by the absence of dose-response relationships, histopathological findings, or clinical signs indicative of liver impairment. Additionally, the observed increases in TBIL, GGT, and decreases in CHOL and UREA in males (25 mg/kg/day) and females (12.5 mg/kg/day), although some were statistically significant, remained within the historical control range. Based on these considerations, it can be agreed that the NOAELs of 25 mg/kg/day for males and 12.5 mg/kg/day for females (at PND70), with AUC values of 532 µg·h/mL and 1100 µg·h/mL respectively, are acceptable.

However, it should be noted that liver toxicity was identified in the 6-month repeat-dose toxicity study in rats (while not in the 28 days study), where hepatocellular vacuolar degeneration and increased liver enzyme activities were observed, indicating hepatobiliary and hepatocellular effects. The NOAELs in that study were 12 mg/kg/day in males and 12.5 mg/kg/day in females, with corresponding AUC values of 390 µg·h/mL and 1120 µg·h/mL (at D90). Furthermore, as stated in the risk management plan, transaminase elevations were

reported in two 52-week Phase 3 studies in cystic fibrosis (CF) patients (6 years and older), suggesting that a contributory role of VNZ/TEZ/D-IVA cannot be excluded. Hepatotoxicity is considered an important identified risk.

While the current juvenile study (PND 7–PND 70) did not identify the liver as a target organ, its limited duration raises uncertainty regarding potential effects with chronic treatment. Thus, the possibility of liver toxicity in juvenile animals cannot be completely ruled out.

**Environmental risk assessment**

Tezacaftor (VX-661) is not PBT, nor vPvB. Based on the data for ivacaftor (VX-770) it can be concluded that deutivacaftor (VX-561) is not PBT nor vPvB.

Tezacaftor is also used in Kaftrio (EMA/473877/2023) and Symkevi (EMA/543681/2020). As tezacaftor is prescribed for the treatment of more than one indication, in more than one product, the $PEC_{sw}$ values for all indications should be calculated and added up to draw conclusions on the environmental risks. As the ERA for IVA is being accepted for D-IVA the same principle applies. Ivacaftor is also used in Kaftrio, Symkevi, Orkambi (EMEA/H/C/003954) and Kalydeco (EMEA/H/C/002494).

Tezacaftor is already used in existing marketed products and no significant increase in environmental exposure is anticipated in view of the rarity of the mutations and number of exposed patients overall.

As the ERA for IVA is being accepted for D-IVA the same principle applies. Ivacaftor is also used in Kaftrio, Symkevi, Orkambi (EMEA/H/C/003954) and Kalydeco (EMEA/H/C/002494).

Ivacaftor/ is already used in existing marketed products and no significant increase in environmental exposure is anticipated for deutivacaftor in view of the rarity of the mutations and number of exposed patients overall.

Vanzacaftor is potentially a PBT substance.

In absence of the full documentation underpinning the Fpen refinement and alignment of the Fpen between the three ingredients, a Phase II assessment and update of the PEC refinement are deemed warranted.

The dossier is not complete as the triggered PBT assessment is not performed and several study reports are not included in the dossier of this ERA.

The environmental risk assessment cannot be concluded pre-approval. It is agreed to provide further information for vanzacaftor post approval.

The applicant has committed to: (i) Perform a PBT assessment and submitting the initial study OECD 308 and interim ERA report in Q3 2025; and (ii) Submit an updated ERA in Q4 2028. Both will be submitted as post authorisation measures.

## 2.4.7. Conclusion on non-clinical aspects

In general, the pharmacology studies demonstrated the mode of action of the triple combination therapy.

Pharmacokinetics and toxicokinetics have been adequately studied for all compounds and in particular the new compounds VNZ and D-IVA. Data collected showed rats and dogs are suitable and relevant animal species for the interpretation of pharmacological and toxicological (safety) findings.

The toxicology profile of the triple combination therapy has been adequately studied

## *2.5. Clinical aspects*

### 2.5.1. Introduction

***GCP aspects***

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

**Table 8. Tabular overview of clinical studies**

| Study ID | Enrolment status<br>Start date<br>Total enrolment/ enrolment goal | Design<br>Control type | Study & control drugs<br>Dose, route of administration and duration<br>Regimen | Population<br>Main inclusion/ exclusion criteria |
|---|---|---|---|---|
| VX18-121-101 | Completed<br><br>30 April 2019<br><br>Part 1: 58/54<br>Part 2: 29/27 | Randomised, double-blind, multi-part<br><br>Part 1: Placebo-controlled<br><br>Part 2: TEZ/IVA-controlled | Part 1:<br>VNZ (Form A)/TEZ/D-IVA<br>5 mg/100 mg/150 mg qd p.o.;<br>10 mg/100 mg/150 mg qd p.o.;<br>20 mg/100 mg/150 mg qd p.o.;<br>Placebo<br>Randomised 1:2:2:1<br><br>4 w + 18 d washout (TEZ/D-IVA or placebo)<br><br>Part 2:<br>VNZ (Form A)/TEZ/D-IVA<br>20 mg qd/100 mg qd/150 mg qd p.o;<br>TEZ/IVA<br>100 mg qd/150 mg q12h p.o.<br>Randomised 2:1<br><br>4 w TEZ/IVA run-in + 4 w VNZ/TEZ/D-IVA or TEZ/IVA + | Inclusion:<br>Confirmed diagnosis of CF;<br>F/MF (Part 1) or F/F genotype (Part 2);<br>≥18 years of age;<br>ppFEV1 ≥40 and ≤90<br><br>Exclusion:<br>Abnormal lab values at screening for haemoglobin, bilirubin, liver function enzymes, or glomerular filtration rate (renal function);<br>Acute respiratory infection;<br>Respiratory infection with organism associated with more rapid decline in pulmonary status |

| | | | | |
|---|---|---|---|---|
| | | | 4 w TEZ/IVA washout | |
| VX18-561-101 | Completed<br><br>17 April 2019<br><br>77/88 | Randomised, double-blind, parallel group, IVA-controlled | D-IVA<br>25 mg qd p.o.;<br>50 mg qd p.o.;<br>150 mg qd p.o.;<br>250 mg qd p.o.;<br>IVA 150 mg q12h p.o.<br>Randomised 1:2:2:2:1<br><br>12 w | Inclusion:<br>Confirmed diagnosis of CF;<br>Gating mutation;<br>≥18 years of age; ppFEV1 ≥40 and ≤100<br><br>Exclusion:<br>Abnormal lab values at screening for haemoglobin, bilirubin, liver function enzymes, or glomerular filtration rate (renal function);<br>Acute respiratory infection;<br>Respiratory infection with organism associated with more rapid decline in pulmonary status |
| VX20-121-102 | Completed<br><br>14 September 2021<br><br>435/400 | Randomised, double-blind, parallel-group, ELX/TEZ/IVA-controlled | VNZ/TEZ/D-IVA<br>20 mg qd/100 mg qd/250 mg qd p.o.;<br>ELX/TEZ/IVA<br>200 mg qd/100 mg qd/150 mg q12h p.o.<br>Randomised 1:1<br><br>4 w ELX/TEZ/IVA run-in + 52 w | Inclusion:<br>Confirmed diagnosis of CF;<br>F/MF genotype;<br>≥12 years of age;<br>ppFEV1 ≥40 and ≤90 for subjects on CFTR modulator treatment or ppFEV1 ≥40 and ≤80 for subjects not on CFTR modulator treatment<br><br>Exclusion:<br>Abnormal lab values at screening for haemoglobin, bilirubin, liver function enzymes, or glomerular filtration rate (renal function);<br>Acute respiratory infection;<br>Respiratory infection with organism associated with more rapid decline in pulmonary status |
| VX20-121-103 | Completed<br><br>27 October 2021<br><br>597/550 | Randomised, double-blind, parallel group, ELX/TEZ/IVA-controlled | VNZ/TEZ/D-IVA<br>20 mg qd/100 mg qd/250 mg qd p.o.;<br>ELX/TEZ/IVA<br>200 mg qd/100 mg qd/150 mg q12h p.o.<br>Randomised 1:1<br><br>4 w ELX/TEZ/IVA run-in + 52 w | Inclusion:<br>Confirmed diagnosis of CF;<br>F/F, F/G, F/RF, or TCR/non-F genotype;<br>≥12 years of age;<br>ppFEV1 ≥40 and ≤90 for subjects on CFTR modulator treatment or ppFEV1 ≥40 and ≤80 for subjects not on CFTR modulator treatment<br><br>Exclusion:<br>Abnormal lab values at screening for haemoglobin, bilirubin, liver function enzymes, or glomerular filtration rate (renal function);<br>Acute respiratory infection;<br>Respiratory infection with organism associated with more rapid decline in pulmonary status |
| VX21-121-105 | Completed<br><br>21 June 2022 | Open label, 2-part | Cohort A1:<br>VNZ/TEZ/D-IVA<br>10 mg/50 mg/125 mg qd p.o. | Inclusion:<br>Confirmed diagnosis of CF;<br>TCR/any genotype;<br>6-11 years of age;<br>ppFEV1 ≥60 |

| | | | | |
|---|---|---|---|---|
| | Cohort A1: 17/12-20<br>Cohort B1: 78/65<br><br>Only Cohorts A1 and B1 for subjects 6-11 y are described; subsequent cohorts planned or ongoing for subjects 1-5 y | | 22 d<br><br>Cohort B1:<br><40 kg at Day 1: VNZ/TEZ/D-IVA 12 mg/60 mg/150 mg qd p.o.<br>≥40 kg at Day 1: VNZ/TEZ/D-IVA 20 mg/100 mg/250 mg qd p.o.<br><br>4 w ELX/TEZ/IVA run-in + 24 w | Exclusion:<br>Abnormal lab values at screening for haemoglobin, bilirubin, liver function enzymes, or glomerular filtration rate (renal function);<br>Acute respiratory infection;<br>Respiratory infection with organism associated with more rapid decline in pulmonary status |

## 2.5.2. Clinical pharmacology

### *2.5.2.1. Pharmacokinetics*

The clinical pharmacology of VNZ/TEZ/D-IVA was characterised using a combination of nonclinical and clinical studies evaluating VNZ and D-IVA monotherapy and the triple combination of VNZ, TEZ, IVA, and/or D-IVA in healthy subjects and/or CF subjects. These data were further supported by prior nonclinical and clinical pharmacology experience with TEZ and IVA from previous development programs for IVA (Kalydeco), TEZ/IVA (Symkevi), and ELX/TEZ/IVA (Kaftrio).

**Methods**

Bioanalytical methods

VNZ, TEZ and its major metabolites (M1-TEZ and M2-TEZ), and D-IVA and its major metabolites (M1-D-IVA and M6-D-IVA) were quantitated using LC-MS/MS methods that were validated to a sufficient extent, with accuracy, specificity and stability meeting appropriate requirements. During sample analysis for VNZ, TEZ and M1-TEZ, as well as D-IVA and M1-D-IVA and M6-D-IVA, Incurred Sample Reanalysis was conducted, yielding satisfactory results.

Pharmacokinetic methods

Standard noncompartmental analyses were used to determine PK parameters in studies where intensive sampling was conducted, and popPK methods were used to characterise exposures of VNZ, TEZ, D-IVA, and relevant metabolites in healthy subjects and CF subjects and to assess the effects of demographic characteristics and other covariates on PK.

Population PK models

PopPK models were developed for VNZ, TEZ, D-IVA and their metabolites. All models were evaluated using prediction-corrected VPC plots.

For VNZ, the presented linear, 1-compartment popPK model with 6 transit compartments and first-order absorption provided a reasonable description of the PK for VNZ. The typical estimate (95% CI) of the VNZ clearance for a reference subject (male with CF, a F/MF genotype, Caucasian, aged 28.9 years, weighing 63.9 kg, with an eGFR of 112 mL/min/1.73m2, ALT of 24.0 U/L, and treated with the Phase 3 VNZ/TEZ/D-IVA TC FDC tablet (VNZ Form D) was 1.23 (1.15-1.32) l/h, which is in reasonable agreement with the observed clearance in healthy subjects of 1.18±0.455 l/h (Study 005). Body weight was a factor that had a clinically meaningful impact on VNZ disposition. Further, a difference in VNZ PK in CF subjects and healthy subject, as well as between VNZ form A and D was accounted for in the model.

For TEZ, the presented 2-compartment model with first-order absorption and an absorption lag time, provided a reasonable description of the PK for TEZ. The typical estimate (95% CI) of the TEZ clearance for a reference subject (weight = 70 kg; genotype = F/MF, F/F, or F/RF and F/other, and treated with the Phase 3 VNZ/TEZ/D-IVA TC FDC tablet) was 1.22 (1.14-1.30) l/h, which is in reasonable agreement with the observed clearance in healthy subjects of 0.937±0.338 l/h (Study 005). For M1-TEZ, the presented 2-compartment model provided a reasonable description of the PK for TEZ. The typical estimate (95% CI) of the M1-TEZ clearance for a reference subject (weight = 70 kg; genotype = F/MF, F/F, or F/RF and F/other, and treated with the Phase 3 VNZ/TEZ/D-IVA TC FDC tablet) was 0.41 (0.40-0.42) l/h. Estimated $C_{max}$ and AUC values for M1-TEZ are within reasonable range for the actually observed data.

For D-IVA, the presented linear, 1-compartment popPK model with 7 transit compartments and first-order absorption, provided a reasonable description of the PK for D-IVA. The typical estimate (95% CI) of the D-IVA clearance for a reference subject (male with CF, a F/MF genotype, White, aged 30 years, weighing 70 kg, with an eGFR of 112 mL/min/1.73m2, ALT of 23.0 U/L, and treated with the Phase 3 VNZ/TEZ/D-IVA triple combination FDC tablet) was 7.03 (6.75-7.31) l/h, which is in reasonable agreement with the observed clearance in healthy subjects of 6.52±2.77 l/h (Study 005).

The popPK models are considered fit-for-purpose, i.e., to describe the disposition of either VNZ, TEZ and M1-TEZ and D-IVA to support dosing recommendations in the triple combination of VNZ/TEZ/D-IVA in specific sub-populations. The impact of the model is considered relatively low.

Physiology-Based PK models

PBPK models were developed and used to expand the conclusions of the VNZ DDI studies related to inhibition of CYP3A4/5. The PBPK model T183 adequately described VNZ plasma concentration-time profiles as well as key PK parameters ($AUC_{last}$ and $C_{max}$) alone and in the presence of itraconazole (up to 264 hours post VNZ co-administration), with the arithmetic mean, 5th, and 95th percentiles capturing the observed profiles to a large extent. The predicted/observed ratio, both without and with itraconazole, are within 0.8 to 1.25 boundaries. The PBPK model is considered fit for purpose, i.e., to predict the maximal impact of extended dosing with a strong CYP3A inhibitor (itraconazole) and the effect of moderate CYP3A inhibitors on the $AUC_{inf}$ and $C_{max}$ of VNZ, based on clinical DDI Study 007.

The D-IVA, M1-D-IVA, M6-D-IVA PBPK model adequately described the concentration-time profiles as well as key PK parameters ($AUC_{inf}$ and $C_{max}$) of D-IVA, and its sequential metabolites M1-D-IVA and M6-D-IVA, when dosed alone or in the presence of itraconazole, with the arithmetic mean, 5th, and 95th percentiles capturing the observed profiles in itraconazole DDI Study 006 to a large extent. The PBPK model is considered fit for

purpose, i.e., to predict the maximal impact of extended dosing with a strong CYP3A inhibitor (itraconazole) and the effect of moderate CYP3A inhibitors on the $AUC_{inf}$ and $C_{max}$ of D-IVA, M1-D-IVA and M6-D-IVA, based on clinical DDI Study 006.

**Absorption**

Following administration with a standard-moderate breakfast in healthy subjects, the median $t_{max}$ for VNZ was 24.00 hours, for TEZ 3.50 hours, and for D IVA 5.08 hours. In CF patients > 12 years of age, based on popPK analysis, VNZ, TEZ, and D-IVA are absorbed with a median (range) time to maximum concentration ($t_{max}$) of approximately 7.80 hours (3.70 to 11.9 hours), 1.60 hours (1.40 to 1.70 hours), and 3.7 hours (2.7 to 11.4 hours), respectively (**Table 9**).

**Table 9. Model-predicted PK parameters from PopPK analyses in CF patients ⩾12 years of age (popPK analyses T270, T271 and T406)**

| Parameter[a] | VNZ | TEZ | D-IVA |
|---|---|---|---|
| Mean±SD $C_{max}$ (µg/mL) | 0.812±0.344 | 6.77±1.24 | 2.33±0.637 |
| Mean±SD $AUC_{0\text{-}24h}$ (µg·h/mL) | 18.6±8.08 | 89.5±28.0 | 39.0±15.3 |
| Mean±SD time to steady state, days | ~20 | NA | NA |
| Mean±SD accumulation ratio | 6.09±1.81 | 1.92±0.337 | 1.74±0.497 |
| Median $t_{max}$ (range), hours | 7.80 (3.70, 11.9) | 1.60 (1.40, 1.70) | 3.7 (2.7, 11.4) |
| Mean±SD effective half-life, hours | 92.8±30.2 | 22.5±5.85 | 19.2±8.71 |
| Mean±SD apparent clearance, L/hours | 1.34±0.819 | 1.22±0.390 | 7.29±2.68 |

[a] Based on multiple doses of VNZ/TEZ/D-IVA tablets in CF subjects receiving VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd.

*Absolute bioavailability*

Absolute bioavailability has not been determined for VNZ, TEZ and D-IVA. Based on mass-balance (TEZ) and food-interaction studies (VNZ, D-IVA), the absolute bioavailability is estimated to be at least 17% (6-fold increased AUC with food) for VNZ, 40% (26% excreted in faeces as metabolite, 14% in urine) for TEZ, and 25% (4-fold increased AUC with high-fat meal) for D-IVA, respectively. Overall, remaining PK studies related to renal and hepatic impairment, as well as DDI, are sufficient to allow the uncertainty on the absolute bioavailability.

*BCS classification*

VNZ and TEZ are considered to be BCS Class 2 (low solubility/high permeability) compounds. Classification of TEZ according to the BCS was previously summarised in the Symkevi (TEZ/IVA) MAA. IVA could not be definitively classified by the BCS (as previously indicated in the IVA MAA). It has low solubility, suggesting that it is either BCS Class 2 (low solubility/high permeability) or Class 4 (low solubility/low permeability). However, its low solubility and nonspecific binding to culture materials precluded an acceptable determination of its permeability using the Caco-2 cell system. Due to the structural similarities between D-IVA and IVA, D-IVA is also expected to be either BCS Class 2 or Class 4.

*Relative bioavailability*

Regarding relative bioavailabilities when VNZ, TEZ, and D-IVA are administered separately or co-administered in triple combination in healthy subjects, exposures of VNZ, TEZ, D-IVA, and their respective metabolites were unchanged when study drug was given single dose but all increased following administration of multiple doses with the triple combination compared to administration of multiple doses as monotherapy. When given as multiple doses in triple combination, VNZ $C_{max}$ and AUC increased 48% and

54%, respectively, TEZ $C_{max}$ and AUC increased 29% and 35%, respectively, and M1-TEZ $C_{max}$ and AUC increased 17% and 11%, respectively. D-IVA $C_{max}$ and AUC increased 18% and 27%, respectively; M1-D-IVA $C_{max}$ and AUC increased 27% and 39%, respectively; and M6-D-IVA $C_{max}$ and AUC increased 41% and 51%, respectively.

Bioequivalence

The bioavailability of the Phase 2 VNZ 20mg/TEZ 100-mg/D-IVA 150-mg FDC tablet and individual VNZ, TEZ and D-IVA tablets has been investigated. TEZ and D-IVA exposures following the 100 and 150 mg dose, respectively, given as FDC tablet were unchanged relative to separate tablets and met bioequivalence criteria. It was shown that exposures from VNZ (Form D) in the FDC tablet at the 20 mg dose level were 50 to 55% lower than exposures from VNZ (Form A) in the individual tablet given at 20 mg. In a subsequent study, exposure to VNZ (Form D) at a 20 mg dose level from the Phase 3/commercial VNZ 10mg/TEZ 50-mg/D-IVA 125-mg FDC tablet was shown to be comparable to that of VNZ at a 10 mg dose level from the individual tablet (Form A), fulfilling 80-125% bioequivalence requirements. The bioequivalence requirements were also fulfilled for TEZ and D-IVA at the 100 mg and 250 mg dose level, respectively.

The paediatric VNZ 4-mg/TEZ 20-mg/D-IVA 50-mg FDC tablets and the VNZ 10mg/TEZ 50-mg/D-IVA 125-mg tablet were compared. AUC and $C_{max}$ ratio's fulfilled bioequivalence requirements 80-125% when administered at the same dose.

Food-effect

The food-effect has been investigated with the final commercial FDC formulation. Both VNZ and D-IVA exposure increased in the presence of food, by 4-6-fold and 3-4-fold, respectively, with more pronounce increase with high fat meals than with low fat meals. Exposure to TEZ was not affected to a relevant extent by food. Since safety does not appear to be a limiting factor, the aim of the applicant to pursue maximal exposure by giving it with food is supported. Although maximum exposure in theory would be obtained by giving the medicinal product with a high fat meal, this situation is not considered acceptable for OD administration. The same posology (with fat-containing food) is also applied for the other related formulations, like Kalydeco, Symkevi and Kaftrio. Further, in the Phase 3 Studies 102, 103, and 105, VNZ/TEZ/D-IVA was administered with fat-containing food.

**Distribution**

Human plasma protein binding is high for VNZ (>99%), TEZ (approximately 99%), and D-IVA (>99%), with albumin being the major human plasma protein for their binding. VNZ and D-IVA also bind to alpha 1-acid glycoprotein.

VNZ, TEZ nor D-IVA do not preferentially partition into red blood cells. After a single oral dose of 2 VNZ 10-mg/TEZ 50-mg/D-IVA 125-mg FDC tablets, the mean±SD apparent volumes of distribution were 90.4±31.3 l for VNZ, 123±43.2 l for TEZ, and 157±47.3 l for D-IVA.

**Elimination**

Information on the elimination of VNZ, TEZ and D-IVA was provided. A new mass balance study was provided for VNZ, whereas for TEZ mass balance data provided earlier in the Symkevi (TEZ/IVA) MAA were available. Both mass balance studies showed adequate recovery of the administered dose.

*VNZ*. Less than 1% of the administrated VNZ dose was excreted in urine as unchanged drug, showing that renal excretion is not the primary pathway of VNZ elimination in humans. A mean of 91.6% of the radioactive dose was recovered in faeces and <0.5% was recovered in urine through the last collection interval, resulting in a mean overall recovery of 92.1%. VNZ is therefore primarily eliminated via the faeces, mainly as metabolite M6-VNZ (26%), as parent compound (<10%) or as M55-VNZ, M19-VNZ, M57-VNZ, and M9-VNZ (7.4%, 6.9%, 6.9%, and 6.8% of the dose, respectively). These results indicate that VNZ is almost exclusively excreted from the body via faeces following oral administration.

*TEZ*. Less than 1% of the administrated TEZ dose was excreted in urine as unchanged drug, showing that renal excretion is not the primary pathway of TEZ elimination in humans. A mean of 72.2% of the radioactive dose was recovered in faeces and 13.7% was recovered in urine through the last collection interval, resulting in a mean overall recovery of 85.9%. TEZ is therefore mainly eliminated via the faeces, either as parent compound (34%) or as M2-TEZ (26% of the administered dose). Renal excretion accounts for approximately 13% of the administered dose (10% as M2-TEZ and 2.5% as M3-TEZ). Less than 1% of the dose is excreted as parent compound via the urine. These results indicate that the majority of TEZ is excreted from the body via faeces following oral administration.

*D-IVA*. No human mass balance study was conducted for D-IVA. Instead, qualitative similarity in absorption, distribution, metabolism, and excretion properties of DIVA and IVA was established by *in vitro* and *in vivo* nonclinical PK and metabolism studies. Nonclinical data indicate that the majority of $^{14}$C-D-IVA and $^{14}$C-IVA are excreted in the faeces, with urine accounting for a minimal proportion of administered radioactivity for both labelled compounds. Major excreted metabolites of D-IVA were M1-D-IVA and M6-D-IVA and major excreted metabolites for IVA were M1-IVA and M6-IVA. The assumption of the applicant, i.e., that based on similar structure of IVA and D-IVA and nonclinical data, the excretion of DIVA in humans is similar to that of IVA is supported. From the original registration Kalydeco (IVA) MAA, it is known that after oral administration of IVA monotherapy, the majority of IVA (87.8%) was eliminated in faeces after metabolic conversion. There was minimal elimination of IVA and its metabolites in urine (only 6.6% of TRA was recovered in the urine). Similar characteristics are expected to be valid for D-IVA.

*Elimination half-life*. Following administration of 2 VNZ (Form D) 10 mg/TEZ 50 mg/D-IVA 125-mg FDC tablets to healthy subjects, the mean±SD terminal $t_{1/2}$ and apparent oral clearance (CL/F) was

For VNZ: 54.0±10.1 hours and 1.18±0.455 l/h.

For TEZ: 92.4±23.1 hours and 0.937±0.338 l/h

For D-IVA: 17.3±2.67 hours and 6.52±2.77 l/h

Based on popPK analyses, the mean ± SD effective half-lives of VNZ, TEZ and D-IVA in CF patients > 12 years of age following administration of the VNZ/TEZ/D-IVA fixed-dose combination tablets are approximately 92.8 ± 30.2 hours, 22.5 ± 5.85 hours and 19.2 ± 8.71 hours, respectively.

**Metabolism**

*VNZ*. *In vitro* metabolism data of VNZ demonstrated that CYP3A4 and CYP3A5 are the CYP isozymes involved in VNZ metabolism. Based on the provided mass-balance Study 004, after a single oral dose of VNZ, unchanged VNZ accounted for the majority of the total circulating radioactivity in plasma (appr 96%), and the only circulating metabolite M19 accounted for less than 10% (appr 3.8%) of the total radioactivity in plasma, indicating that there are no major circulating metabolites of VNZ. Therefore, VNZ parent is expected to be solely responsible for activity, without relevant contributions from VNZ metabolites.

*TEZ*. Based on data provided for the Symkevi (TEZ/IVA) MAA, TEZ and TEZ-M1 are known to be metabolised mainly by CYP3A4 and CYP3A5. Following oral administration of a single dose of 100 mg $^{14}$C-tezacaftor to healthy male subjects, M1-TEZ, M2-TEZ, and M5-TEZ were the 3 major circulating metabolites of TEZ in humans (contributing to 15%, 31%, and 33% of total radioactivity, respectively). TEZ represents 7% of total radioactivity. M1-TEZ has similar potency to that of tezacaftor and is considered pharmacologically active. M2-TEZ is much less pharmacologically active than tezacaftor or M1-TEZ, and M5-TEZ is not considered pharmacologically active. A minor circulating metabolite, M3-TEZ, is formed by direct glucuronidation of tezacaftor. Therefore, TEZ and M1-TEZ are considered collectively responsible for activity.

*D-IVA*. Like IVA, D-IVA is mainly metabolised by CYP3A4 and CYP3A5. *In vivo*, it was shown that the same metabolites were detected in human plasma of subjects that received D-IVA as the ones that received IVA, except for the presence of deuterium where appropriate (so M1(-D)-IVA and M6(-D)-IVA as major metabolites). D-IVA appeared to exhibit somewhat more metabolic stability than IVA. M1-D-IVA has approximately one-fifth the potency of D-IVA and is considered pharmacologically active. M6-D-IVA is the other major metabolite of D-IVA, a deuterated equivalent of M6-IVA, and is not considered pharmacologically active. Clinical activity of D-IVA is therefore considered governed both by parent D-IVA and the M1-D-IVA metabolite.

Pharmacokinetics of metabolites

*VNZ metabolites*. No information is provided on the PK of VNZ metabolite M19. This is considered acceptable, considering the low abundance of this metabolite as compared to parent VNZ (3.8% vs total radioactivity in plasma)

*D-IVA metabolites*. Pharmacokinetics of the major metabolites of D-IVA, M1-D-IVA and M6-D-IVA, has been investigated to a reasonable extent. $T_{max}$ for both metabolites is approximately 5-6 hours post-dosing of D-IVA, and steady state for both metabolites appears to be reached after 5 days of once daily dosing. No increased accumulation of the metabolites as compared to parent D-IVA is observed. Under steady-state, exposure to active metabolite M1-D-IVA is comparable to somewhat lower than that of D-IVA, whereas exposure to the inactive metabolite M6-D-IVA is somewhat lower than D-IVA.

**Dose proportionality and time dependencies**

*VNZ*. Exposure to VNZ (administered as monotherapy or in combination with TEZ and D-IVA) increases in an approximately dose-proportional manner with increasing doses from 5 to 60 mg once daily.

*TEZ*. Data from the Symkevi MAA indicated that exposure to TEZ (administered alone or in combination with IVA) increases in an approximately dose-proportional manner with increasing doses from 10 mg to 300 mg once daily.

*D-IVA*. After multiple ascending doses of D-IVA in the fed state, D-IVA AUC increased approximately dose proportionally from 50 to 250 mg once daily.

In CF patients, based on popPK analysis, plasma concentrations reach steady state within 20 days of OD daily dosing for VNZ, within 8 days for TEZ, and within 8 days for D-IVA.

The accumulation ratio in healthy subjects was 3.5 to 5.5 for VNZ and 1.2 to 1.7 for D-IVA. Based on popPK analyses, the accumulation ratio in CF patients of approximately 6 for VNZ is in line with the $t_{1/2}$ of approximately 54 h. Likewise, the lower accumulation ratio observed for D-IVA of 1.74 and for TEZ of 1.92 is in line with their $t_{1/2}$ of approximately 20 h.

PK variability

Overall, inter subject variability for VNZ, TEZ and D-IVA was moderate to high, ranging from approximately 18% to 41% for VNZ, 13% to 34% for TEZ, and 16% to 65% for D-IVA.

Pharmacokinetics in the target population

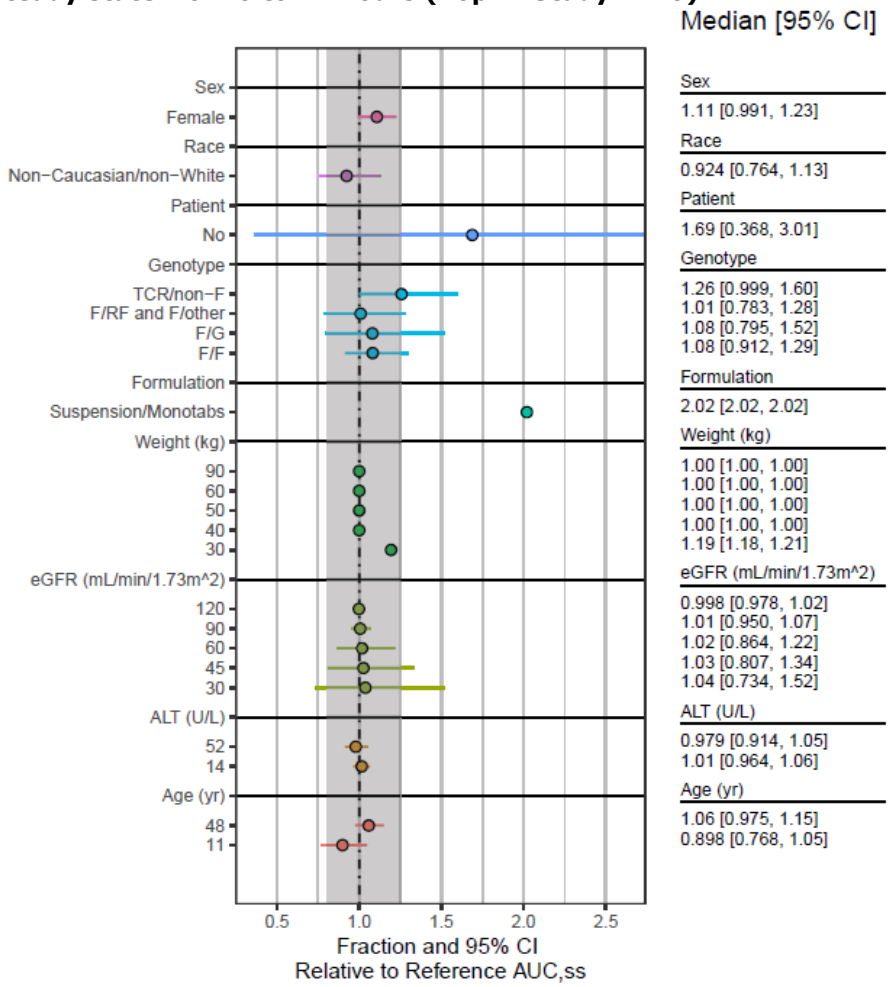
In general, exposure (AUC, $C_{max}$) to VNZ, TEZ and D-IVA in CF patients was comparable to that in healthy volunteers. The PK parameters for VNZ, TEZ and D-IVA in CF patients ⩾12 years of age, estimated using PK data from all clinical studies in a combined fashion, are summarised in Table 9.

**Special populations**

The effect of intrinsic factors like disease state (e.g., healthy compared to CF subjects) and demographics (e.g., weight, age, renal function, hepatic function, race, and sex) on VNZ, TEZ, and D-IVA PK were assessed using PopPK analysis based on data from Phase 3 Studies 102, 103, and 105.

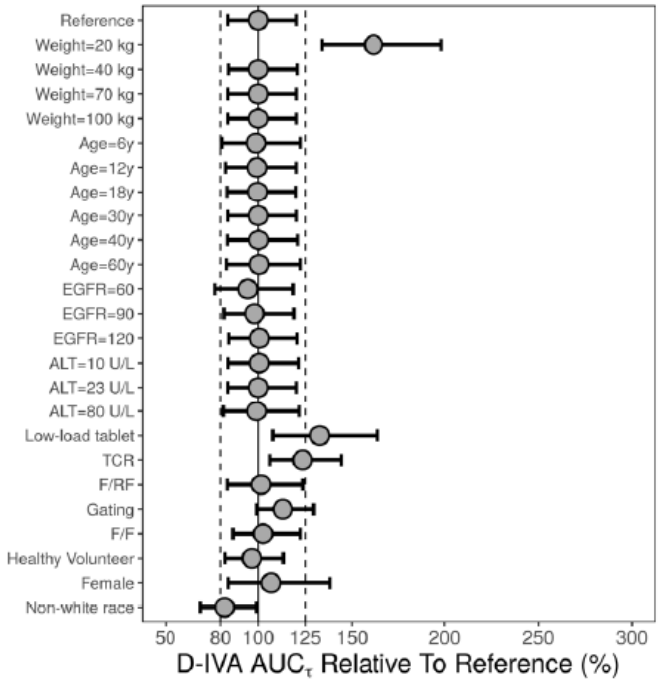
Weight was identified as the key covariate having a clinically meaningful impact on VNZ, TEZ, and D-IVA disposition and informed the dose selection. Covariate forest plots for VNZ and D-IVA AUC at steady state from 0 to 24 hours from popPK Study T270 and T460 are shown in Figure 4 and Figure 5, respectively).

**Figure 4. Full Model: Covariate forest plot for VNZ area under the concentration-time curve at steady state from 0 to 24 hours (PopPK Study T270)**




The full model covariate effects were visualised by varying single covariates individually while keeping all other conditions constant. Results are presented relative to a reference subject, i.e., male with CF, a F/MF genotype, Caucasian, aged 28.9 years, weighing 63.9 kg, with an eGFR of 112 mL/min/1.73m2, ALT of 24.0 U/L, and treated with the Phase 3 VNZ/TEZ/D-IVA TC FDC tablet (VNZ Form D). The coloured circles represent the median and the solid horizontal lines represent the 95% confidence interval (CI). The grey shaded area is the reference range with a lower bound of 0.8 and an upper bound of 1.25.

**Figure 5. D-IVA Covariate model: forest plot for the full model (PopPK Study T406)**




Notes: The full model covariate effects were visualised by varying single covariates individually while keeping all other conditions constant. Results are presented relative to a reference subject, i.e., male with CF, a F/MF genotype, White, aged 30 years, weighing 70 kg, with an eGFR of 112 mL/min/1.73m2, ALT of 23.0 U/L, and treated with the Phase 3 VNZ/TEZ/D-IVA TC FDC tablet. The circles represent the typical value and the solid horizontal lines represent the 95% confidence interval (CI). The grey shaded area is the reference range with a lower bound of 0.8 and an upper bound of 1.25.

*Impaired renal function*. Collectively, PK results provided for VNZ, TEZ and D-IVA suggest that renal clearance is likely to play a minimal role in the elimination of VNZ, TEZ, and D-IVA. No dose adjustment of VNZ/TEZ/D-IVA is recommended for people with CF with mild to moderate renal impairment. In the absence of clinical data, however, caution is recommended when administering VNZ/TEZ/D-IVA to people with CF with severe renal impairment (eGFR <30 mL/min/1.73 $m^2$) or with end-stage renal disease.

*Impaired hepatic function*. In the dedicated hepatic impairment Study 008 it was shown that after a single oral dose of VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg FDC tablet, the impact of MHI on TEZ exposures were minimal while the mean exposures of VNZ and D-IVA were, respectively, 30% and 20% lower in subjects with MHI when compared with matched healthy subjects. The following proposed dose recommendations in the SmPC are proposed:

- Mild hepatic impairment (Child Pugh Class A, score 5 to 6): No dose adjustment is recommended. Liver function tests should be closely monitored.
- MHI (Child Pugh Class B, score 7 to 9): Use of VNZ/TEZ/D-IVA is not recommended and should only be considered when there is a clear medical need and the benefit exceeds the risk. If used, no dose adjustment is required.
- Severe hepatic impairment (Child Pugh Class C, score 10 to 15): VNZ/TEZ/D-IVA should not be used.

*Gender*. Based on popPK, there are no clinically relevant differences in exposures of VNZ, TEZ and D-IVA between male and female CF subjects.

*Ethnic factors*. Based on popPK, there are no clinically relevant differences in exposures of VNZ and D-IVA between White and non-White CF subjects.

*Weight*. Body weight was determined to have an impact on exposure of VNZ, TEZ, D-IVA, and their metabolites. The effect of weight on the PK of VNZ, TEZ, D IVA, and their metabolites is considered to be clinically meaningful for patients aged 6 through 11 years of age weighing <40 kg and based on PopPK simulations, a weight-based dose is proposed, i.e., 150/60/12 mg D-IVA/TEZ/VNZ for subjects <40 kg and 250/100/20 mg D-IVA/TEZ/VNZ for subjects ≥40 kg.

*Elderly*. No discussion was provided by the applicant. Instead, a global reference was made to popPK reports for VNZ, TEZ and D-IVA.

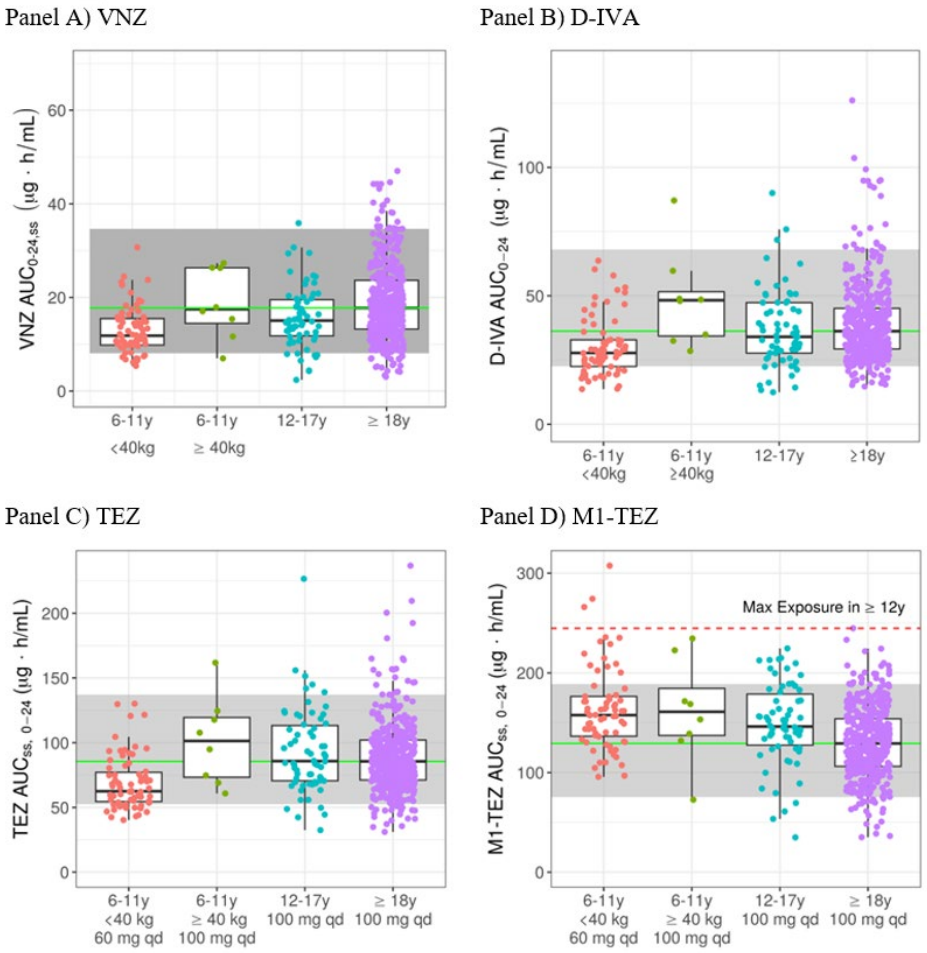
*Paediatric population*. The steady-state AUC values of VNZ, TEZ, M1 TEZ, and D-IVA in CF paediatric subjects 6 through 11 years of age, adolescents, and adults are summarised in Table 10 and compared graphically in Figure 6.

**Table 10. Summary of VNZ, TEZ, M1 TEZ, and D-IVA observed steady-state AUC by age group (From PopPK Studies T270 (VNZ), T271 (D-IVA) and T406 (TEZ)**

| | | VNZ $AUC_{0-24h}$ (µg·h/mL) | | | TEZ $AUC_{0-24h}$ (µg·h/mL) | | | M1-TEZ $AUC_{0-24h}$ (µg·h/mL) | | | D-IVA $AUC_{0-24h}$ (µg·h/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age Group, Weight** | **Dose Regimen (VNZ/TEZ/D-IVA)** | **N** | **Mean (SD)** | **Min, Max** | **N** | **Mean (SD)** | **Min, Max** | **N** | **Mean (SD)** | **Min, Max** | **N** | **Mean (SD)** | **Min, Max** |
| 6 through 11 years | (Both doses combined) | 78 | 13.6 (5.43) | 5.37, 30.7 | 78 | 72.4 (24.2) | 40.3, 162 | 78 | 163 (42.8) | 72.7, 308 | 78 | 32.1 (13.5) | 13.7, 87.1 |
| <40 kg | 12 mg qd/ 60 mg qd/ 150 mg qd | 70 | 13.0 (4.90) | 5.37, 30.7 | 70 | 69.1 (20.7) | 40.3, 130 | 70 | 163 (42.2) | 95.7, 308 | 70 | 30.2 (11.6) | 13.7, 63.7 |
| ⩾40 kg | 20 mg qd/ 100 mg qd/ 250 mg qd | 8 | 18.6 (7.49) | 6.99, 27.3 | 8 | 101 (33.7) | 60.8, 162 | 8 | 162 (51.5) | 72.7, 235 | 8 | 48.5 (18.7) | 28.5, 87.1 |
| 12 through 17 years | 20 mg qd/ 100 mg qd/ 250 mg qd | 66 | 15.8 (6.52) | 2.39, 35.9 | 66 | 93.0 (32.5) | 32.5, 227 | 66 | 149 (41.2) | 35.0, 225 | 65 | 37.1 (15.3) | 12.5, 90 |
| ⩾18 years | 20 mg qd/ 100 mg qd/ 250 mg qd | 414 | 19.0 (8.22) | 3.04, 47.0 | 414 | 89.0 (27.2) | 31.1, 237 | 414 | 130 (35.2) | 35.1, 245 | 413 | 39.3 (15.3) | 14.7, 126 |

D-IVA: deutivacaftor; max: maximum value; min: minimum value; N: total sample size; qd: once daily; TEZ: tezacaftor; VNZ: vanzacaftor

**Figure 6. Steady-state AUC versus age group for VNZ, D-IVA, TEZ, and M1-TEZ, applying a weight cut-off for dose adjustment of 40 kg (PopPK Studies T270 (VNZ), T271 (TEZ) and T406 (D-IVA))**




D-IVA: deutivacaftor; EBE: empirical Bayes estimate; IQR: interquartile range; qd: once daily; TEZ: tezacaftor; VNZ: vanzacaftor; y: years of age
Notes: Adults and adolescents received VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg qd dose, subjects 6 through 11 years of age ≥40 kg received VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg qd dose, and subjects 6 through 11 years of age <40 kg received VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg qd dose. Green horizontal line represents the median of the adult values and the grey shaded area indicates the 5th and 95th percentiles of the adult values. Points represent individual EBE values. Boxplots present statistics of the points, with the median represented by a horizontal line, and the IQR represented by a box. The whiskers mark the largest and smallest values within 1.5 × IQR.

VNZ, TEZ, and D-IVA exposures in the 6 to less than 18 years of age are within the range observed in adults with CF.

In the proposed SmPC, VNZ/TEZ/D-IVA in paediatric subjects 6-11 years is to be administered with fat-containing food as follows:

- People with CF ≥6-11 years of age weighing ≥40 kg: VNZ 20 mg qd/TEZ 100 mg qd/D IVA 250 mg qd
- People with CF ≥6-11 years of age weighing <40 kg: VNZ 12 mg qd/TEZ 60 mg qd/D IVA 150 mg qd.

The applicant provided comparisons of exposure to tezacaftor, vanzacaftor and deutivacaftor and M1-TEZ in the 6-11 years age group as compared to the adult values, applying either a 40 kg or a 30 kg cut-off (See Figure 7). For tezacaftor, vanzacaftor and deutivacaftor, the exposures in patients 6-11 years of age are

within the 5th and 95th percentiles of the adult exposures, however, new data for M1-TEZ were provided, indicating exposures for the active M1-TEZ metabolite to be higher than the adult exposures in case of a 30 kg cut-off. In case of a 40 kg cut-off, the M1-TEZ exposure was within the range of adult exposures.

**Figure 7. Comparison of VNZ, TEZ, M1-TEZ, and D-IVA Steady-state AUC by Age and Dose Group for the 40 kg and 30 kg Weight Cutoffs**

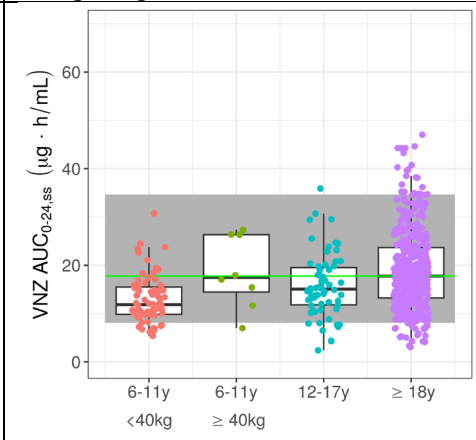
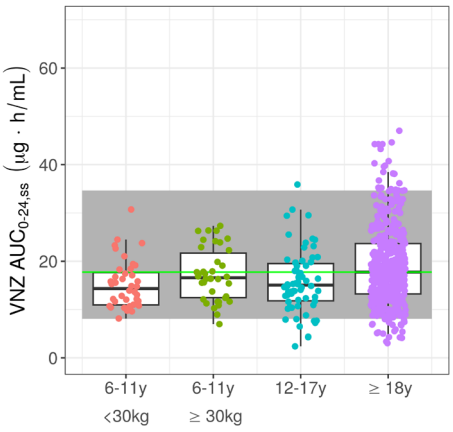
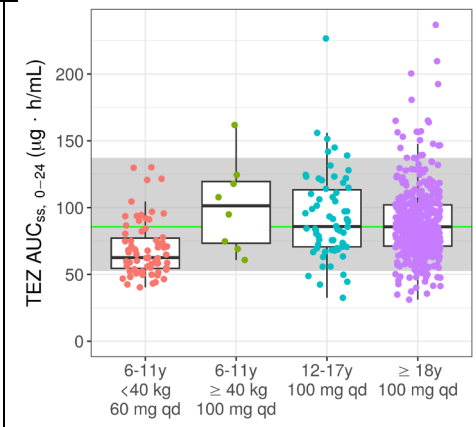
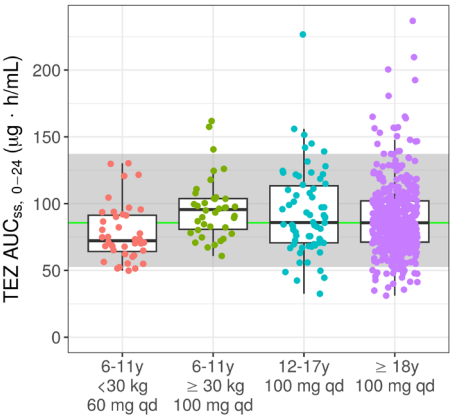
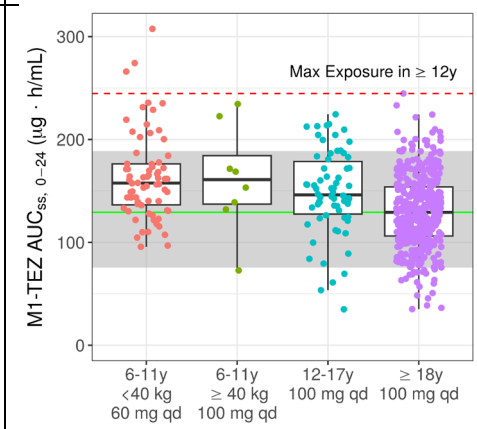
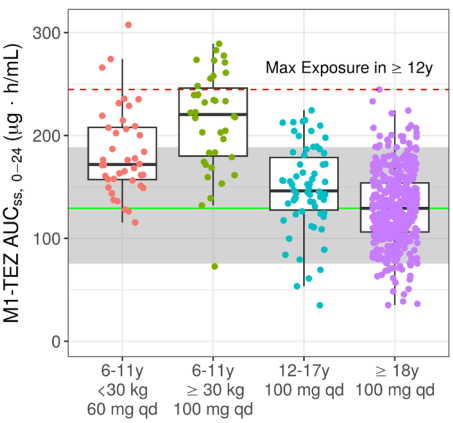
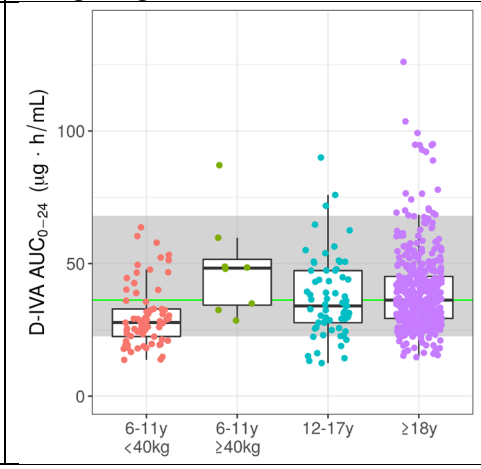
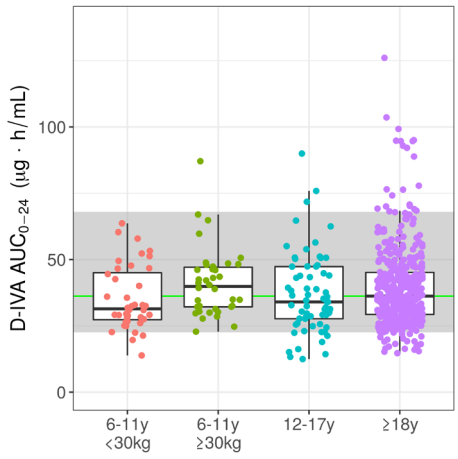
| Analyte | 40 kg weight cutoff | 30 kg weight cutoff |
|---|---|---|
| VNZ |  |  |
| TEZ |  |  |
| M1-TEZ |  |  |

**Figure 7. Comparison of VNZ, TEZ, M1-TEZ, and D-IVA Steady-state AUC by Age and Dose Group for the 40 kg and 30 kg Weight Cutoffs**

| Analyte | 40 kg weight cutoff | 30 kg weight cutoff |
|---|---|---|
| D-IVA |  |  |



40 kg weight cutoff sources: Report T270/Figure 10 (VNZ), Report T271/Figures 14 (TEZ) and 23 (M1-TEZ), Report T406/Figure 11.136 (D-IVA)
30 kg weight cutoff sources: Report T270/Figure S96 (VNZ), Report T271/Figures S63 (TEZ) and S164 (M1-TEZ), Report T406/Figure 11.145 (D-IVA)
EBE: empirical Bayes estimate; D-IVA: deutivacaftor; IQR: interquartile range; TEZ: tezacaftor; VNZ: vanzacaftor; y: years of age
Notes: Green horizontal line represents the median of the adult values and the grey shaded area indicates the 5th and 95th percentiles of the adult values. Boxplots: median is represented by a horizontal line, and the IQR is represented by a box. The whiskers mark the largest and smallest values within 1.5 × IQR. Dots represent individual EBE values.

General information on the baseline body weight of the adolescent patients enrolled in Studies 102 and 103, as well as body weight for children aged 6 years to less than 12 years old in Study 105 was provided. Minimum weight for the 6–12-year-old patients in clinical studies was reported as 19.3 kg. Further, exposure was predicted down to a weight of 15.4 kg, being the 5th percentile for weight in this patient population.

**Pharmacokinetic interaction studies**

*In vitro substrate characteristics*. *In vitro*, all observed metabolites of VNZ resulted from oxidative metabolism by CYP3A4/5. There are no major circulating metabolites of VNZ in human, metabolite M19, present at only 3.8% of total peak area, is the main metabolite.

From the Symkevi (TEZ/IVA) MAA it is known that TEZ undergoes both Phase I and Phase II metabolism to form M1-TEZ (a dehydrogenated metabolite), M2-TEZ (a sequentially oxidised metabolite of M1-TEZ), M5-TEZ (a phosphate conjugate of M1-TEZ), and glucuronides of TEZ and M1-TEZ. CYP3A4/5 are the main enzymes involved in the oxidative metabolism of TEZ.

Similar to IVA, D-IVA is primarily metabolised by oxidation to form the 2 major circulating metabolites, M1-D-IVA and M6-D-IVA, the deuterated equivalents of M1-IVA and M6-IVA. CYP3A4/5 are the main enzymes involved in the oxidative metabolism of D-IVA and IVA.

*In vitro inhibition*. For VNZ, TEZ and D-IVA, based on *in vitro* data, no *in vivo* DDI related to inhibition of CYP enzymes by VNZ, TEZ or D-IVA is expected. For this conclusion, the ICH M12 cut-off was used. The applicant followed a more conservative approach, and does not exclude relevant inhibition *in vivo* for CYP2B6, CYP2C8,

and CYP2C9 by VNZ, and for CYP1A2, CYP2B6, CYP2C19, and CYP2D6 by D-IVA, M1-D-IVA and M6-D-IVA. In line with the information in the SmPC of IVA (Kalydeco), IVA/TEZ (Symkevi) and IVA/TEZ/EXE (Kaftrio), information on potential inhibition of CYP2C9 is included in the SmPC. Such interaction may be relevant for NTI drugs like warfarin. Some of these potential DDIs have been investigated *in vivo*, indicating no relevant inhibition by any of these *in vitro* suggested CYPs.

*In vitro induction*. Based on *in vitro* data, no *in vivo* DDI related to induction of CYP enzymes by VNZ, TEZ or D-IVA is expected.

*In vitro transporters*. VNZ is not a substrate of P-glycoprotein (P-gp), BCRP, OATP1B1, or OATP1B3. VNZ has low potential to inhibit P-gp efflux of digoxin at clinically relevant concentrations, and it may inhibit BCRP. VNZ has low potential to inhibit OATP1B1 or OATP1B3 uptake and is predicted to have weak inhibition of OAT1. VNZ did not inhibit OAT3, OCT1/2, or MATE1/2-K *in vitro*.

As known from the Symkevi MAA, TEZ and M1 TEZ are P-gp substrates. TEZ is a substrate for OATP1B1, but not for OATP1B3. M2-TEZ is a substrate for the uptake transporters OATP1B1 and OATP1B3. M2-TEZ appears to be a P gp substrate, but data are not conclusive. TEZ, M1 TEZ, M2 TEZ, and M5 TEZ were weak P-gp inhibitors *in vitro*. TEZ, M1 TEZ, M2-TEZ, and M5-TEZ have low potential to inhibit OATP1B1 and OATP1B3.

D-IVA and M1 D-IVA are substrates of P-gp and BCRP but are not substrates of OATP1B1 or OATP1B3. M6-D-IVA is not a substrate of P-gp, but is a substrate of OATP1B1, OATP1B3, and BCRP. D-IVA and M1 D-IVA are P-gp inhibitors. D-IVA showed similar P-gp inhibition potency as IVA *in vitro* and is expected to have comparable P-gp inhibition *in vivo*. D-IVA has low potential to inhibit OATP1B1 and OATP1B3. Since *in vitro* transporter inhibition data for IVA and D-IVA were similar and the clinical DDI risks for IVA have been characterised to be relatively small, the DDI risk of D-IVA is predicted to be similarly low.

VNZ/TEZ/D-IVA was not evaluated for concomitant use with P gp substrates. However, from the Symkevi (TEZ/IVA) MAA it is known that *in vivo* co administration of TEZ/IVA with digoxin, a sensitive P gp substrate, increased digoxin AUC by 1.3-fold. This is indicated in the Symkevi and Kaftrio SmPC. Therefore, also for VNZ/TEZ/D-IVA, it is indicated in the SmPC that this FDC may increase systemic exposure of medicinal products that are sensitive substrates of P gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P gp with a narrow therapeutic index such as cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used. This information in section 4.5 is agreed.

*In silico*. VNZ, TEZ, and D-IVA are all extensively metabolised by CYP3A. Therefore, based on PBPK simulations, VNZ, TEZ, and D-IVA exposures are predicted to be reduced by concomitant CYP3A inducers and are increased by concomitant CYP3A inhibitors (i.e., by 10.5-, 4 to 4.5-, and 11.1-fold for VNZ, TEZ and D-IVA by the strong CYP3A inhibitor itraconazole and by 2.4 to 3.9-, 2.1- and 2.9 to 4.8-fold for VNZ, TEZ and D-IVA by moderate CYP3A inhibitors).

To account for the increase in exposures to VNZ, TEZ and D-IVA in the presence of strong and moderate inhibitors of CYP3A, a reduction in the dose of VNZ/TEZ/D-IVA is recommended, which is based on PBPK simulations. The applicant has chosen to tailor the advice on the actives with the most pronounced increase in exposure with a potent inhibitor of CYP3A (i.e., 10.5-fold increase for VNZ and 11.1-fold for D-IVA). Overall, the dose advice, '*reduce the dose to 1 FDC tablet (VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg) once a week for subjects ≥40 kg and to 2 FDC tablets (VNZ 8 mg/TEZ 40 mg/D-IVA 100 mg) once a week for subjects <40 kg*', yielded simulated VNZ and D-IVA exposures in the mid-range of exposures observed in the absence of an inhibitor of CYP3A. The same holds for the advice in the case of moderate inhibitors of CYP3A

(‘*reduce the dose to 1 FDC tablet (VNZ 10 mg/TEZ 50 mg/D IVA 125 mg) every other day for subjects ≥40 kg and to 2 FDC tablets (VNZ 8 mg/TEZ 40 mg/D-IVA 100 mg) every other day for subjects <40 kg’*).

*In vivo drug interactions.*

*Effect of co-administered drugs on VNZ/TEZ/D-IVA in vivo.* VNZ, TEZ, and D-IVA are all extensively metabolised by CYP3A. Therefore, VNZ, TEZ, and D-IVA exposures are expected to be reduced by concomitant CYP3A inducers and are increased by concomitant CYP3A inhibitors (i.e., by 10.5-, 4 to 4.5-, and 11.1-fold for VNZ, TEZ and D-IVA by the strong CYP3A inhibitor itraconazole and by 2.4 to 3.9-, 2.1- and 2.9 to 4.8-fold for VNZ, TEZ and D-IVA by moderate CYP3A inhibitors, based on combined in vivo DDI Study and PBPK). Dose advice in case of potent or moderate CYP3A inhibitor co-medication are proposed. Further, due to the expected decrease in exposure to VNZ, TEZ and D-IVA by the concomitant use of CYP3A inducers, co administration with strong CYP3A inducers is not recommended in the SmPC.

*Effect of VNZ/TEZ/D-IVA on co-administered drugs in vivo. CYP2C9 substrates.* Based on *in vitro* data and in the absence of *in vivo* data, D-IVA may inhibit CYP2C9. Therefore, monitoring of the international normalised ratio (INR) during co administration of VNZ/TEZ/D-IVA with warfarin is recommended. Other CYP2C9 substrate medicinal products for which exposure may be increased i.e. glimepiride and glipizide should be used with caution. This information is provided in the SmPC section 4.5, which is acceptable.

*Potential for interaction with transporters. P-gp.* VNZ/TEZ/D-IVA was not evaluated for concomitant use with P gp substrates. However, from the previous Symkevi MAA, it is known that co administration of TEZ/IVA with digoxin, a sensitive P gp substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by TEZ and IVA. Therefore, administration of VNZ/TEZ/D-IVA may increase systemic exposure of medicinal products that are sensitive substrates of P gp, which may increase or prolong their therapeutic effect and adverse reactions. In the SmPC section 4.5 it is stated that ‘when used concomitantly with digoxin or other substrates of P gp with a narrow therapeutic index such as cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used’. This wording is considered acceptable.

*OATP1B1*. Based on *in vitro* data, VNZ, TEZ, and D-IVA have low potential to inhibit OATP1B1 at clinically relevant concentrations. D-IVA has a similar OATP1B1 inhibition potential to IVA *in vitro*. However, based on an *in vivo* DDI study of TEZ/IVA with pitavastatin, an OATP1B1 substrate, no clinically relevant effect on the exposure of pitavastatin was observed.

Hormonal contraceptives

Since no relevant inhibition of CYP3A was noted *in vitro*, VNZ/TEZ/D-IVA is not expected to have an impact on the efficacy of oral contraceptives. Although the currently requested product VNZ/TEZ/D-IVA was not evaluated for concomitant use with oral contraceptives, TEZ in combination with IVA and IVA alone have been studied with ethinyl oestradiol/norethindrone. In both situations, these were found to have no clinically relevant effect on the exposures of the oral contraceptive. This information is sufficiently worded in the SmPC section 4.5.

**Relationship between plasma concentration and effect and safety**

VNZ exposure-effect relationships were investigated towards ppFEV1 and SwCl. For ppFEV1, a flat exposure-effect relation was observed, however, for SwCl, a further decrease was noted at the higher 20 mg VNZ dose as compared to lower doses. The PD effect of VNZ was measured when given in combination with TEZ and D-IVA, which may introduce uncertainty towards the PD effect being related to VNZ or the other active

substances administered. Still, the relationship for SwCl and VNZ exposure is apparent, so in that sense the 20 mg VNZ dose studied in the pivotal Phase 3 studies is supported by the E-R results for VNZ.

With respect to D-IVA, PopPK/PD modelling further supports the somewhat increased efficacy of D-IVA 250 mg qd treatment compared to D-IVA 150 mg qd, as the 250 mg qd dose provided near-maximal benefit for both SwCl and ppFEV1. However, the differences between the 150 mg and 250 mg D-IVA dose are considered small, and the 250 mg D-IVA dose instead of the 150 mg dose chosen for further development in the Phase 3 studies is not beyond discussion. However, The D-IVA 250 mg qd dose was generally safe and well tolerated with safety profile similar to IVA 150 mg q12h, so the 250 mg D-IVA dose is considered acceptable for use in the Phase 3 study and this dose is supported by the provided E-R analyses.

Evaluation and Qualification of PK/PD Models

The population models describing the exposure-response relationship of ppFEV1 and SwCl were developed using the empirical Bayes estimates from previously developed popPK models. The different PK/PD model fit the ppFEV1 and SwCl data reasonably well.

Dose justification

*Subjects > 12 years of age.* The dosing regimen of VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd was selected based on safety and E-R analyses of Phase 2 Studies 101 and 561-101. In these studies, and the related E-R analyses, the exposure from VNZ 20 mg qd (form D) was predicted to result in near-maximal improvements in SwCl (97% of $E_{max}$) and was also shown to be safe and well-tolerated. Study 101 was conducted with the form A VNZ formulation. It is agreed that the outcome for the 10 mg form A is valid for the final 20 mg form D formulation. Therefore, a 20 mg qd dose (Form D) of VNZ was used in Phase 3 studies in subjects ⩾12 years of age.

The TEZ dose of 100 mg qd is consistent with approved dosing regimens for TEZ/IVA and ELX/TEZ/IVA.

The exposure from D-IVA 250 mg qd was predicted to result in near-maximal benefits (e.g., 82% to 84% of $E_{max}$) over the studied dose range for both SwCl and $ppFEV_1$ and was predicted to be more efficacious compared to a D-IVA 150 mg qd dose.

Overall, the dose-selection for the pivotal Phase 3 studies was conducted in a satisfactory manner, taking into account E-R relationships, formulation characteristics and previous experience.

*Subjects 6 through 11 years of age.* Exposure simulations in subjects 6 through 11 years of age showed that the following dose regimen with a 40 kg weight cutoff was appropriate for this population in Study 105 Cohort B1:

- Subjects weighing ⩾40 kg received VNZ 20 mg (Form D)/TEZ 100 mg/D-IVA 250 mg qd (100% of the adult dose); and
- Subjects weighing <40 kg received VNZ 12 mg (Form D)/TEZ 60 mg/D-IVA 150 mg qd (60% of the adult dose)

Overall, the results of these simulations demonstrated that a 40 kg cutoff would result in VNZ, TEZ, and D-IVA exposures similar to exposures in subjects ⩾18 years of age while maintaining M1 TEZ exposures that are either within the range of prior clinical experience or remain below the safety margins from nonclinical toxicology studies.

#### *2.5.2.2. Pharmacodynamics*

**Mechanism of action**

**Primary and Secondary pharmacology**

**Primary pharmacology**

Sweat chloride concentration is a direct measure of CFTR function in the sweat gland that is used as a PD marker of on-target activity of CFTR modulators. The percentage predicted Forced Expiratory Volume in 1 second (ppFEV1) is used as a clinical parameter. The dose finding studies will be briefly described in section 6.3.4 Clinical efficacy.

**Secondary pharmacology**

The effect of VNZ on QT/QTc interval was investigated in a double-blind, randomised, placebo- and active-controlled, parallel with nested crossover, multiple-dose ECG study following doses of VNZ (Form A) 10 and 60 mg qd. A total of 56 healthy male and female subjects were randomised 2:1:1 to 1 of 3 treatment groups. Group 1 received VNZ 10 mg qd for 7 days, followed by 60 mg qd for 7 days. A nested crossover design was utilised for moxifloxacin and placebo in Groups 2A and 2B.

Serial ECGs and matching PK samples were collected for assessment of VNZ and moxifloxacin plasma concentrations. Continuous ECGs were extracted in up to 10 replicates predose on Days -1, 1, 8, 15, and 16, and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 23.5 hours post-dose (Days 2, 9, and 17). The primary analysis of ΔQTcF for therapeutic and supratherapeutic doses of VNZ was based on C-QTc analysis of VNZ. Assay sensitivity was evaluated by C-QTc analysis of moxifloxacin on ΔQTcF.

VNZ did not have an effect on the QTc interval in Study VX22-121-013.

LS mean change-from-baseline QTcF (ΔQTcF) on VNZ closely followed the placebo pattern across post-dose time points on both Day 11 (10 mg qd) and Day 21 (60 mg qd)). LS mean placebo-corrected ΔQTcF (ΔΔQTcF) across post-dose time points on both days varied from -1.9 ms (at 10 hours post-dose on Day 21 in the 60 mg dose group) to 2.2 ms (at 6 hours post-dose on Day 11 in the 10 mg dose group), without an indication of dose- or concentration-dependency. On Day 21, with the highest VNZ concentrations, LS mean ΔΔQTcF varied between -1.9 ms at 10 hours and 1.6 ms at 2 and 3 hours post-dose.

The estimated population slope of the VNZ concentration-QTc relationship was -0.000025 ms per ng/mL (90% CI: -0.0005597 to 0.0005102) with a treatment effect-specific intercept of 0.28 ms (90% CI: -2.367 to 2.936). Neither the treatment effect-specific intercept nor the slope was statistically significant at the 10% level (P values of 0.8582 and 0.9382, respectively).

Assay sensitivity was demonstrated by the moxifloxacin C-QTc relationship with a statistically significant slope and by demonstrating that the predicted effect at Cmax was above 5 msec.

VNZ at the studied doses did not have an effect on heart rate, pulse rate, or QRS intervals.

## 2.5.3. Discussion on clinical pharmacology

The clinical pharmacology of VNZ/TEZ/D-IVA was characterised using a combination of nonclinical and clinical studies evaluating VNZ and D-IVA monotherapy and the triple combination of VNZ, TEZ, IVA, and/or D-IVA in

healthy subjects and/or CF subjects. These data were further supported by prior nonclinical and clinical pharmacology experience with TEZ and IVA from previous development programs for IVA (Kalydeco), TEZ/IVA (Symkevi), and ELX/TEZ/IVA (Kaftrio).

Applied bioanalytical methods are validated to a sufficient extent and fit for purpose. In addition, the popPK models are considered fit-for-purpose, i.e., to describe the disposition of either VNZ, TEZ and M1-TEZ and D-IVA to support dosing recommendations in the triple combination of VNZ/TEZ/D-IVA in specific sub-populations, the impact of the model is considered relatively low. Further, the PBPK models are considered fit-for-purpose, i.e., to predict the impact of strong or moderate CYP3A inhibitors on exposure ($AUC_{inf}$ and $C_{max}$) for VNZ or D-IVA and its metabolites, as expansion of actual vivo DDI Study 007 (VNZ and itraconazole) and Study 006 (D-IVA and itraconazole).

*Food-effect*. The food-effect has been investigated with the final commercial FDC formulation. Both VNZ and D-IVA exposure increased in the presence of food, by 4-6-fold and 3-4-fold, respectively, with more pronounced increase with high fat meals than with low fat meals. Exposure to TEZ was not affected to a relevant extent by food. Since safety does not appear to be a limiting factor, the aim of the applicant to pursue maximal exposure by giving it with food is supported. Although maximum exposure in theory would be obtained by giving the medicinal product with a high fat meal, this situation is not considered acceptable for OD administration. The same posology (with fat-containing food) is also applied for the other related formulations, like Kalydeco, Symkevi and Kaftrio. Further, in the Phase 3 Studies 102, 103, and 105, VNZ/TEZ/D-IVA was administered with fat-containing food.

Thus, the proposed posology, i.e., to give VNZ/TEZ/D-IVA with fat-containing food, is considered acceptable.

*Relative bioavailability*. With regard to relative bioavailabilities when VNZ, TEZ, and D-IVA are administered separately or co-administered in triple combination in healthy subjects, exposures of VNZ, TEZ, D-IVA, and their respective metabolites were unchanged when study drug was given single dose but all increased following administration of multiple doses with the triple combination compared to administration of multiple doses as monotherapy. When given in triple combination, VNZ $C_{max}$ and AUC increased 48% and 54%, respectively, TEZ $C_{max}$ and AUC increased 29% and 35%, respectively, and M1-TEZ $C_{max}$ and AUC increased 17% and 11%, respectively. D-IVA $C_{max}$ and AUC increased 18% and 27%, respectively; M1-D-IVA $C_{max}$ and AUC increased 27% and 39%, respectively; and M6-D-IVA $C_{max}$ and AUC increased 41% and 51%, respectively. Although it is not clear why relative exposure to VNZ, TEZ and D-IVA in Study 005 following single dose is comparable, however increased in Study 006 after multiple dose, it is agreed with the applicant that the increases are unlikely to be clinically meaningful, as effective concentration levels of ppFEV1 and SwCl for VNZ, TEZ, and D-IVA did not change appreciably when administered in triple combination compared to monotherapy, based on E-R modelling. Of note, the Phase 3 exposures of VNZ, TEZ, and D-IVA were similar to the Phase 2 exposures, based on which the doses for Phase 3 were selected.

*Consequences of possible genetic polymorphism*. Although reports have appeared on a polymorphism for CYP3A4, i.e. CYP3A4*22, contradictory results have been published on the relevance of this polymorphism. At this stage evidence is considered not sufficient to require further information on this.

*Elimination half-life*. The applicant claims that $t_{1/2}$ of D-IVA is longer than of IVA. This would make D-IVA suitable for OD administration, whereas IVA is to be dosed BID. In that respect, apparently the applicant compared the effective $t_{1/2}$ of IVA and D-IVA in CF patients. However, although preclinical data may suggest increased stability of D-IVA vs IVA, the previously reported $t_{1/2}$ of IVA in CF patients was 9.3±1.7h (Symkevi) and 13.1±2.98h (Kaftrio), which does not appear to be clearly different from the reported $t_{1/2}$ of D-IVA of 19.2±8.71h, considering the variations in $t_{1/2}$ that are often observed between different studies. However,

since the clinical studies have been conducted with the OD posology for D-IVA and it is unlikely that the clinical outcome would be markedly different when D-IVA would have been given BID, this issue will not be further pursued.

Therapeutic window

The applicant argues that there are no defined minimal clinically important differences for ppFEV1 or SwCl, which is line with current opinions. Instead, exposure matching was used in order to achieve similar exposures in different subpopulations, applying the 5th to 95th percentiles of the adult exposure range. This is considered an acceptable approach in this situation. The use of PKPD simulations in case exposures were not contained within this 5th to 95th percentiles of the adult exposure range is in principle supported.

However, although it is agreed that no EU clinical consensus guideline is available, in previous CHMP procedures for CF products like Orkambi, Symkevi and Kaftrio, a 2-3% change in ppFEV1 and 10 mml/l SwCl have been applied. Using these previously applied therapeutic margins, the applicant was invited to provide the no effect boundaries/therapeutic margin which represent the interval within which a change in systemic exposure measure to VNZ, TEZ or D-IVA that is considered not significant enough to warrant clinical action. The applicant did not provide such no effect boundary and considered exposure-matching to be sufficient. This issue was noted by CHMP and not pursued by CHMP in this application.

Special populations

*Impaired renal function*. Collectively, PK results provided for VNZ, TEZ and D-IVA suggest that renal clearance is likely to play a minimal role in the elimination of VNZ, TEZ, and D-IVA. No dose adjustment of VNZ/TEZ/D-IVA is recommended for people with CF with mild to moderate renal impairment. In the absence of clinical data, however, caution is recommended when administering VNZ/TEZ/D-IVA to people with CF with severe renal impairment (eGFR <30 mL/min/1.73 $m^2$) or with end-stage renal disease. These recommendations are included in the proposed SmPC section 4.2 and are the same as those for Symkevi (TEZ/IVA) and Kalydeco (IVA).

*Impaired hepatic function*. In the dedicated hepatic impairment Study 008 it was shown that after a single oral dose of VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg FDC tablet, the impact of MHI on TEZ exposures were minimal while the mean exposures of VNZ and D-IVA were, respectively, 30% and 20% lower in subjects with MHI when compared with matched healthy subjects. The following proposed dose recommendations in the SmPC are proposed:

- Mild hepatic impairment (Child Pugh Class A, score 5 to 6): No dose adjustment is recommended. Liver function tests should be closely monitored.
- MHI (Child Pugh Class B, score 7 to 9): Use of VNZ/TEZ/D-IVA is not recommended and should only be considered when there is a clear medical need and the benefit exceeds the risk. If used, no dose adjustment is required.
- Severe hepatic impairment (Child Pugh Class C, score 10 to 15): VNZ/TEZ/D-IVA should not be used.

The information in the SmPC is partly consistent with the recommendations for Symkevi (TEZ/IVA) and (Kaftrio) ELX/TEZ/IVA. For Symkevi , Kalydeco and Kaftrio, a dose reduction is proposed for subjects with MHI. The reason for the difference with the current application is that exposure to IVA and IVA/ELX increased for Symkevi and Kaftrio, respectively, whereas for the current VNZ/TEZ/D-IVA product, a decrease in exposure was observed for VNZ and D-IVA. Therefore, based on the provided data, the proposed dose-advice in case of MHI are supported. The applicant discussed why exposure to IVA increases with impaired hepatic

function whereas exposure to D-IVA decreases. The apparent difference can be explained by multiple factors, mainly, variability in the effect of moderate hepatic impairment (MHI) observed historically with IVA and in Study 008 for D-IVA, as well as D IVA improved metabolic stability compared to IVA. In summary, no single explanation appears conclusive for the apparent difference in effect of hepatic impairment on IVA and D-IVA,

It is agreed that the effect of hepatic impairment on IVA, has been variable, an effect that can be expected with small studies like the hepatic impairment studies. The 90% CI of the effect for D-IVA partly overlaps with the 90% of some other hepatic impairment studies with IVA.

*Ethnic factors*. There are no clinically relevant differences in exposures of VNZ and D-IVA between White and non-White CF subjects. In section 5.2 of the SmPC, the following is proposed by the applicant:

- Race had no clinically meaningful effect on VNZ exposure based on population PK analysis in whites (N = 664) and non-whites (N = 44). The non-white races consisted of 9 Black or African Americans, 7 Asians, 7 with multiple racial background, 2 American Indian or Alaska Native, 2 with other ethnic background, and 17 not collected.
- Very limited population PK data indicate comparable exposure of TEZ in whites (N = 652) and non-whites (N = 8). The non-white races consisted of 5 Blacks or African Americans and 3 Native Hawaiians or other Pacific Islanders.
- Race had no clinically meaningful effect on the PK of D-IVA in whites (N = 670) and non-whites (N = 41) based on a population PK analysis. The non-white races consisted of 18 Black or African Americans, 2 Asians, 3 with multiple racial background, 1 with other ethnic background, and 17 not collected.

In principle the way of reporting was agreed, however, for verification purposes, the applicant provided details on the source of the indicated figures in the SmPC.

*Elderly*. Upon request a discussion on the PK in elderly was provided by the applicant. The number of elderly subjects >65 years of age is very limited (n=2), which is expected in light of the indication. Very limited data suggest no differences in PK of VNZ, TEZ and D-IVA in elderly as comparted to adult patients. The lack of information in elderly subjects is now mentioned in section 4.4 of the SmPC, which is agreed.

**Table 11. Age ranges studied in the elderly population**

| | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| Study 102 | 0/196 | 0/196 | 0/196 |
| Study 103 | 2/284 | 0/284 | 0/284 |

*Paediatric population*. In the proposed SmPC, VNZ/TEZ/D-IVA in paediatric subjects 6-11 years is proposed to be administered with fat-containing food as follows:

- People with CF ≥6-11 years of age weighing ≥40 kg: VNZ 20 mg qd/TEZ 100 mg qd/D IVA 250 mg qd
- People with CF ≥6-11 years of age weighing <40 kg: VNZ 12 mg qd/TEZ 60 mg qd/D IVA 150 mg qd.

With the proposed dose-recommendations, exposure to VNZ, TEZ and D-IVA in the different subcategories ≥6-11 years and ≥40 kg, ≥6-11 years and <40 kg, and 12-18 years is in reasonable agreement with that observed in adults. Mean M1-TEZ exposure was 25% higher for subjects 6 through 11 years of age than the mean exposure for adults. This finding is consistent with that observed in the TEZ/IVA clinical development programme and can also in this case be accepted.

The proposed cut-off for an adjusted dose of 40 kg is different than the 30 kg cut-off, as registered for Symkevi and Kaftrio. Further, the dose of TEZ in the Kalydeco, Symkevi and Kaftrio SmPC for children below 30 kg (i.e., 50% of the adult dose) is different from the dose proposed for DEU/TEZ/D-IVA for children below 40 kg (i.e. 60%of the adult dose).

A roughly comparable relative increased exposure for M1-TEZ in children was observed in the previous dossiers for Symkevi (TEZ/IVA) and Kaftrio (EXE/TEZ/IVA). Also in this case, exposure for M1-TEZ was somewhat higher than that observed in adults. However, for Symkevi and Kaftrio the effect appeared slightly less pronounced that for the current application. This may partly be related to the fact that the dose reduction for Symkevi and Kaftrio in patients <30 kg was larger (i.e. to 50% of the adult dose) than the dose reduction for VNZ/DEU/TEZ (i.e. to 60% of the adult dose).

The applicant provided information on the predicted exposures for the proposed posology with a 40 kg cut-off in children 6 years of age who are either in the 5th percentile for weight (16.69 kg) or at the lightest weight for the age group (15.40 kg). Applying the proposed posology, VNZ, TEZ, and D-IVA exposures are within the range of exposures in adults in Phase 3 studies. For the active M1-TEZ metabolite, exposure is increased as compared to that in adults. However, exposures to M1-TEZ in low-weight children 6 years of age are in line with those observed for Kaftrio (ELX/TEZ/IVA) triple combination in the Phase 3 subjects 2 years of age and older. This is considered sufficient justification for the posology proposed with a 60% of the adult dose for patients <40 kg of weight.

Although arguments to also use a 30 kg cut-off for VNZ/DEU/TEZ in the current application are valid, e.g. in order to avoid confusion and dosing errors in young patients, based on the current findings, indicating a higher exposure for M1-TEZ in patients aged 6-11 years as compared to adults upon dosing with VNZ/DEU/TEZ with a 30 kg cut-off, the chosen cut-off of 40 kg is considered acceptable by CHMP.

Pharmacokinetic interaction studies

*In vitro substrate characteristics. In vitro*, all observed metabolites of VNZ resulted from oxidative metabolism by CYP3A4/5. There are no major circulating metabolites of VNZ in human, metabolite M19, present at 3.8% of total peak area, is the main metabolite.

From the Symkevi (TEZ/IVA) MAA it is known that TEZ undergoes both Phase I and Phase II metabolism to form M1-TEZ (a dehydrogenated metabolite), M2-TEZ (a sequentially oxidised metabolite of M1-TEZ), M5-TEZ (a phosphate conjugate of M1-TEZ), and glucuronides of TEZ and M1-TEZ. CYP3A4/5 are the main enzymes involved in the oxidative metabolism of TEZ.

Similar to IVA, D-IVA is primarily metabolised by oxidation to form the 2 major circulating metabolites, M1-D-IVA and M6-D-IVA, the deuterated equivalents of M1-IVA and M6-IVA. CYP3A4/5 are the main enzymes involved in the oxidative metabolism of D-IVA and IVA.

Concluding, a relevant effect of inhibition of CYP3A4/5 cannot be excluded, based on *in vitro* information.

*OATP*. Although based on *in vitro* data, VNZ, TEZ, and D-IVA have low potential to inhibit OATP1B1 at clinically relevant concentrations, since co administration of TEZ/IVA with pitavastatin, an OATP1B1

substrate, had no clinically relevant effect on the exposure of pitavastatin no dose advice or caution is indicated for this combination. This is agreed.

*In silico*. VNZ, TEZ, and D-IVA are all extensively metabolised by CYP3A. Therefore, based on PBPK simulations, VNZ, TEZ, and D-IVA exposures are predicted to be reduced by concomitant CYP3A inducers and are increased by concomitant CYP3A inhibitors (i.e., by 10.5-, 4 to 4.5-, and 11.1-fold for VNZ, TEZ and D-IVA by the strong CYP3A inhibitor itraconazole and by 2.4 to 3.9-, 2.1- and 2.9 to 4.8-fold for VNZ, TEZ and D-IVA by moderate CYP3A inhibitors).

To account for the increase in exposures to VNZ, TEZ and D-IVA in the presence of strong and moderate inhibitors of CYP3A, a reduction in the dose of VNZ/TEZ/D-IVA is recommended, which is based on PBPK simulations. The applicant has chosen to tailor the advice on the active substances with the most pronounced increase in exposure with a potent inhibitor of CYP3A (i.e., 10.5-fold increase for VNZ and 11.1-fold for D-IVA). Overall, the dose advice, '*reduce the dose to 1 FDC tablet (VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg) once a week for subjects ≥40 kg and to 2 FDC tablets (VNZ 8 mg/TEZ 40 mg/D-IVA 100 mg) once a week for subjects <40 kg*', yielded simulated VNZ and D-IVA exposures in the mid-range of exposures observed in the absence of an inhibitor of CYP3A. The same holds for the advice in the case of moderate inhibitors of CYP3A ('*reduce the dose to 1 FDC tablet (VNZ 10 mg/TEZ 50 mg/D IVA 125 mg) every other day for subjects ≥40 kg and to 2 FDC tablets (VNZ 8 mg/TEZ 40 mg/D-IVA 100 mg) every other day for subjects <40 kg'*). In both cases, however, due to the lesser effect of inhibition of CYP3A on TEZ exposure, the exposure of TEZ after the proposed dose-correction is lower than observed in the absence of an inhibitor of CYP3A. This situation is different from the situation for Symkevi and Kaftrio, where a specific higher dose reduction could be applied from IVA, since this was given twice daily, as compared to TEZ or ELX/TEZ once daily. In fact, for Symkevi and Kaftrio, a specific dose-reduction was possible for TEZ and ELX/TEZ (the latter having a comparable effect of inhibition of CYP3A4 as TEZ). The clinical relevance of the lower exposure to TEZ in case of co-administering at a lower dose with a moderate or strong inhibitor of CYP3A4 was further discussed. Additional PKPD analyses were conducted, indicting comparable PD effect of VNZ/TEZ/D-IVA when combined with a moderate or strong CYP3A4 inhibitor. Details on the additional PKPD models and its validation were not provided, however, that the E-R relationship for TEZ was shown to be relatively flat based on previous submissions. Further, it is agreed with the applicant that a lesser reduction of the VNZ/TEZ/D-IVA dose in the presence of an inhibitor of CYP3A4 could potentially lead to unsafe exposures to VNZ and D-IVA. Therefore, CHMP considered sufficiently justified that the lower TEZ exposure when VNZ/TEZ/D-IVA is given at a lower dose in the presence of a moderate or strong inhibitor of CYP3A4 does not affect PD of VNZ/TEZ/D-IVA in a pronounced way, and the proposed dose adjustments described in section 4.2 of SmPC in the presence of a moderate or strong inhibitor of CYP3A4 are agreed.

In vivo drug interactions

*Effect of co-administered drugs on VNZ/TEZ/D-IVA.* For TEZ/IVA (Symkevi), it was shown that ciprofloxacin, a moderate CYP3A inhibitor, had no clinically relevant effect on exposure of TEZ or IVA when administered as TEZ/IVA. VNZ and D-IVA are expected to be impacted by ciprofloxacin coadministration to a similar or lesser extent than IVA. Therefore, no dose adjustment is necessary during concomitant administration of VNZ/TEZ/D-IVA with ciprofloxacin, and this is indicated in the SmPC. This recommendation is consistent with the recommendations for ELX/TEZ/IVA, TEZ/IVA, and IVA and is therefore agreed.

*Effect of co-administered drugs on VNZ/TEZ/D-IVA.* VNZ, TEZ, and D-IVA are all extensively metabolised by CYP3A. Therefore, VNZ, TEZ, and D-IVA exposures are expected to be reduced by concomitant CYP3A inducers and are increased by concomitant CYP3A inhibitors (i.e., by 10.5-, 4 to 4.5-, and 11.1-fold for VNZ, TEZ and D-IVA by the strong CYP3A inhibitor itraconazole and by 2.4 to 3.9-, 2.1- and 2.9 to 4.8-fold for

VNZ, TEZ and D-IVA by moderate CYP3A inhibitors). Dose advice in case of potent or moderate CYP3A inhibitor co-medication are proposed. Further, due to the expected decrease in exposure to VNZ, TEZ and D-IVA by the concomitant use of CYP3A inducers, co administration with strong CYP3A inducers is not recommended in the SmPC. The applicant argued that induction by moderate inducers of CYP3A4 is expected to yield exposures which may be too low to yield adequate efficacy. Additional PBPK investigations were further conducted, indicating also markedly reduced exposures (approximately 70%) to VNZ, TEZ and D-IVA in the presence of the moderate inducer efavirenz. Thus the applicant proposed to update the SmPC to also mark moderate inducers of CYP3A4 as not recommended. This is supported by CHMP.

Dose justification

*Subjects > 12 years of age.* The dosing regimen of VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd was selected based on safety and E-R analyses of Phase 2 Studies 101 and 561-101. In these studies and the related E-R analyses, the exposure from VNZ 20 mg qd (form D) was predicted to result in near-maximal improvements in SwCl (97% of $E_{max}$) and was also shown to be safe and well-tolerated. Study 101 was conducted with the form A VNZ formulation, having a 2-fold higher bioavailability than the final Form D. It is agreed that the outcome for the 10 mg form A is valid for the final 20 mg form D formulation. Therefore, a 20 mg qd dose (Form D) of VNZ was used in Phase 3 studies in subjects $\geqslant$12 years of age.

The TEZ dose of 100 mg qd is consistent with approved dosing regimens for TEZ/IVA and ELX/TEZ/IVA.

The exposure from D-IVA 250 mg qd was predicted to result in near-maximal benefits (e.g., 82% to 84% of $E_{max}$) over the studied dose range for both SwCl and $ppFEV_1$ and was predicted to be more efficacious compared to a D-IVA 150 mg qd dose.

Overall, the dose-selection for the pivotal Phase 3 studies was conducted in a satisfactory manner, taking into account E-R relationships, formulation characteristics and previous experience.

*Subjects 6 through 11 years of age.* After finalisation of the Phase 3 clinical trials, comparable exposure in subjects <40 kg and > 40 kg was confirmed in the final popPK Studies T270 (VNZ), T271 (D-IVA) and T406 (TEZ).

Overall, the dose-selection for the pivotal Phase 3 studies in children was conducted in a satisfactory manner, taking into account the available data prior to start of the Phase 3 study, E-R relationships, formulation characteristics and previous experience.

Effect of VNZ on QT/QTc interval

VNZ was assessed for QT prolongation as monotherapy. IVA and TEZ have been evaluated previously in dedicated thorough QT studies; the results showed that treatment with IVA or TEZ at therapeutic or supratherapeutic doses did not have clinically significant effects on QTc. The assessment of the monocomponent is considered acceptable based on the ICH guideline E14, that states that, in general, combinations of two or more drugs are unlikely to need a thorough QT/QTc study or intensive late-stage monitoring, if the component drugs have been demonstrated to lack relevant effects in thorough QT/QTc studies.

There were no indications of an effect of VNZ on cardiac repolarisation. Mean ΔQTcF values were negative at all post-dose time points in the active treatment group. For mean ΔQTcF values and mean placebo corrected ΔQTcF (ΔΔQTcF), the 95% CI did not exceed 10 ms at any timepoint. A QTcF effect (ΔΔQTcF) above 10 msec based on the upper bound of the 90% CI can be excluded up to a VNZ plasma concentration of approximately

8 µg/ml. These concentrations are approximately 10-fold higher than mean VNZ $C_{max}$ values (approximately 0.8±0.3 µg/mL) in subjects with CF following VNZ 10 mg qd Form A or 20 mg Form D.

Assay sensitivity was adequately demonstrated by the moxifloxacin concentration-QTc relationship with a statistically significant slope and by demonstrating that the predicted effect at Cmax was above 5 msec. The results showed that VNZ did not have an effect on the QTc interval and did not have a clinically relevant effect on HR or cardiac conduction.

## 2.5.4. Conclusions on clinical pharmacology

Overall, the clinical pharmacodynamics and pharmacokinetics of VNZ/TEZ/D-IVA have been investigated to a reasonable extent.

## 2.5.5. Clinical efficacy

### *2.5.5.1. Dose-response studies*

A total of two randomised phase 2 dose response were conducted:

- study VX18-561-101
- study VX18-121-101

**Study VX 18-561-101; D-IVA**

Study VX18-561-101 was a randomised, double-blind, IVA-controlled, parallel-group, multicentre study in CF subjects 18 years and older with a gating mutation. This monotherapy dose-ranging study was conducted to establish efficacy, PD, PK, safety and tolerability of D-IVA for Phase 3.

Subjects received either D-IVA (25 mg qd, 50 mg qd, 150 mg qd, or 250 mg qd) or IVA 150 mg every 12 hours (q12h) for 12 weeks.

A total of 77 CF subjects were enrolled aged ⩾18 years who harboured at least one of the following CFTR mutations i. e. G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. The subject had a forced expiratory volume in 1 second (FEV1) ⩾40% and ⩽100% standard predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI]) at the Screening Visit.

The study was originally designed to investigate at least 4 doses of D-IVA, i.e., 25 mg qd, 50 mg qd 150 mg or 250 mg qd. However, during the conduct of the trial the applicant received reports of 5 subjects who experienced a decrease in ppFEV1; 4 of these subjects discontinued study drug. Based on this data, the applicant decided to discontinue both D-IVA 25 mg qd and 50 mg qd treatment groups.

Key efficacy results from study 561-101 for the 150 mg and 250 mg qd are summarised in Table 12.

**Table 12. Efficacy and PD of D-IVA treatment relative to IVA Baseline**

| Treatment Group | Absolute Change in $ppFEV_1$ in percentage points at Week 12 (LS mean [95% CI]) | Absolute Change in SwCl in mmol/L at Week 12 (LS mean [95% CI]) |
|---|---|---|
| D-IVA 250 mg qd | 2.7 (-1.0, 6.5) | -6.5 (-14.1, 1.2) |
| D-IVA 150 mg qd | 3.1 (-0.8, 7.0) | 3.3 (-4.6, 11.2) |
| IVA 150 mg q12h | -0.8 (-6.2, 4.7) | 0.9 (-9.5, 11.3) |

D-IVA: deutivacaftor; IVA: ivacaftor; LS: least squares; PD: pharmacodynamic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; qd: once daily; SwCl: sweat chloride

**VX18-121-101; Part 1: dose finding VNZ; Part 2: establish effect VNZ/TEZ/IVA**

Study 101 was a randomised, phase 2 double-blind, placebo- and TEZ/IVA-controlled, parallel-group, multicentre study in F/MF (Part 1) and F/F subjects (Part 2) 18 years and older. The study evaluated safety, tolerability, efficacy, PD and PK of VNZ (VX-121 Form A) in combination with TEZ/D-IVA.

In Part 1, F/MF subjects received VNZ (Form A; 5, 10, or 20 mg once daily [qd]) in TC with TEZ 100 mg qd/D-IVA 150 mg qd or placebo for 4 weeks, followed by TEZ/IVA or placebo for 18 days washout period.

In Part 2, F/F subjects received TEZ/IVA for 4 weeks during the run-in period, followed by the TC of VNZ (Form A) 20 mg qd/TEZ 100 mg qd/D-IVA 150 mg qd or TEZ/IVA for 4 weeks, followed by TEZ/IVA for 4 weeks washout period.

Key efficacy results from study 101 are summarised in Table 10. VX-121/TEZ/D-IVA treatment for 4 weeks in subjects with F/MF (part 1) or F/F genotypes (part 2) resulted in improvements in ppFEV1 (primary efficacy endpoint) and SwCl and CFQ-R RD score (Table 13).

**Table 13. Key efficacy results of trial VX18-121-101 part 1 (F/MF) and part 2 (F/F)**

| Study Part | Treatment Group | Absolute Change From Baseline in $ppFEV_1$ Through Day 29 in percentage points | Absolute Change From Baseline in SwCl Through Day 29 in mmol/L | Absolute Change From Baseline in CFQ-R RD Score At Day 29 in points |
|---|---|---|---|---|
| Part 1; LS mean (SE) | TC-5 mg | 4.6 (3.0) | -42.8 (4.4) | 17.6 (7.0) |
| | TC-10 mg | 14.2 (2.1) | -45.8 (3.0) | 21.2 (4.7) |
| | TC-20 mg | 9.8 (2.0) | -49.5 (3.2) | 29.8 (4.4) |
| | Placebo | 1.9 (3.0) | 2.3 (4.6) | 3.3 (6.7) |
| Part 2; LS mean (SE) | TC-20 mg | 15.9 (2.3) | -45.5 (2.0) | 19.4 (4.3) |
| | TEZ/IVA | -0.1 (3.0) | -2.6 (2.8) | -5.0 (5.8) |

CFQ-R: Cystic Fibrosis Questionnaire – Revised; D-IVA: deutivacaftor; IVA: ivacaftor; LS: least squares; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; qd: once daily; RD: respiratory domain; SwCl: sweat chloride; TC: triple combination; TC-5 mg: VX-121 5 mg qd/TEZ 100 mg qd/D-IVA 150 mg qd; TC-10 mg: VX-121 10 mg qd/TEZ 100 mg qd/D-IVA 150 mg qd; TC-20 mg: VX-121 20 mg qd/TEZ 100 mg qd/D-IVA 150 mg qd; TEZ: tezacaftor

Notes: Within-group LS means (SE) compared to baseline are presented. Baseline in Part 2 was established after a 4-week TEZ/IVA Run-in Period.

### *2.5.5.2. Main studies*

**Studies 102 and 103**

**Study VX20-121-102**: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VNZ Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for F508del and a Minimal Function Mutation (F/MF).

**Study VX20-121-103**: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VNZ Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for F508del, Heterozygous for F508del and a Gating (F/G) or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive CFTR Mutation and No F508del Mutation.

**Methods**

Study design

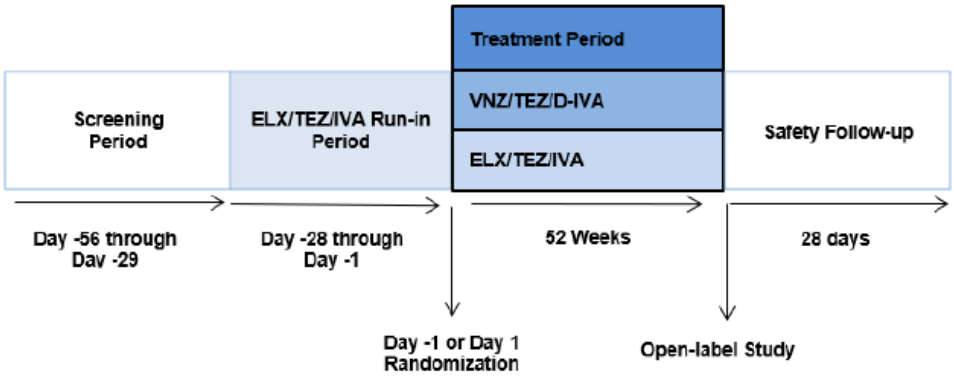
*Study 102*

Following a 4-week ELX/TEZ/IVA Run-in Period, **F/MF subjects** ≥12 years of age were randomised 1:1 to receive either VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd or ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h. Randomisation was stratified by age at the Screening Visit (<18 versus ≥18 years of age), ppFEV1 determined during the Run-in Period (Day -14 clinic assessment; <70 versus ≥70 percentage points), SwCl determined during the Run-in Period (Day -14 assessment; <30 versus ≥30 mmol/L), and prior CFTR modulator use (yes versus no).

*Study 103*

Following a 4-week ELX/TEZ/IVA Run-in Period, **F/F, F/G, F/RF, and TCR/non-F subjects** ≥12 years of age were randomised 1:1 to receive either VNZ/TEZ/D-IVA or ELX/TEZ/IVA. Randomisation was stratified by age at the Screening Visit (<18 versus ≥18 years of age), ppFEV1 determined during the Run-in Period (Day -14 clinic assessment; <70 versus ≥70 percentage points), SwCl determined during the Run-in Period (Day -14 assessment; <30 versus ≥30 mmol/L), and prior CFTR modulator use (yes versus no), and genotype group (F/F, F/G, F/RF, and TCR/non-F).

**Figure 8. Study schema (Studies 102 and 103)**




D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor

Study Participants

The main inclusion criteria were, in both studies, age 12 years and older, FEV1 value ≥40% and ≤90% (or ≤80% for subjects not on ELX/TEZ/IVA treatment) and stable CF. Diagnosis of CF was confirmed by the investigator. The only difference was CFTR genotype:

Study 102 included subjects heterozygous for F508del and a minimal function mutation (defined as a Class I minimal function mutation [i.e. mutations that produce no protein]) (F/MF).

Study 103 included subjects homozygous for F508del (F/F), heterozygous for F508del and a gating (Class III) (F/G) or residual function (Class IV or V) (F/RF) mutation or have at least 1 other triple combination responsive mutation and no F508del mutation (TCR/non-F).

Exclusion criteria were similar in both studies and included abnormal lab values of haemoglobin, bilirubin, or liver function enzymes, acute respiratory infection, lung infection with organisms associated with a more rapid decline in pulmonary status, renal impairment (glomerular filtration rate ≤50 mL/min/1.73 m2 for subjects ≥18 years and ≤45 mL/min/1.73 m2 for subjects 12-17 years) and moderate or severe hepatic impairment (Child Pugh Score B or C).

Treatments

The treatment regimens used in Studies 102 and 103 were similar and are summarised in Table 14. Both VNZ/TEZ/D-IVA and ELX/TEZ/IVA were provided as fixed-dose combination tablets given as morning dose, supplemented with an evening dose of IVA (ELX/TEZ/IVA regimen) or matching placebo (VNZ/TEZ/D-IVA regimen). All study drugs were taken within 30 minutes of the start of a fat-containing meal or snack.

**Table 14. Treatment period groups and dosages**

| Treatment Group | VX-121 | ELX | TEZ | D-IVA | IVA |
|---|---|---|---|---|---|
| VX-121/TEZ/D-IVA | 20 mg qd | 0 mg | 100 mg qd | 250 mg qd | 0 mg |
| ELX/TEZ/IVA | 0 mg | 200 mg qd | 100 mg qd | 0 mg | 150 mg q12h |

D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Note: Study drug administration is described in Section 9.6.

Objectives and endpoints

The primary objective was to evaluate the efficacy of VNZ/TEZ/D-IVA in:

- CF subjects ≥12 years of age with an F/MF genotype – Study 102;
- CF subjects ≥12 years of age with an F/F, F/G, F/RF, or TCR/non-F genotype – Study 103.

The primary endpoint was absolute change from baseline in ppFEV1 through Week 24, which was tested for non-inferiority, applying a non-inferiority margin of 3.0 percentage points. The primary null hypothesis was that the mean absolute change in ppFEV1 from baseline through Week 24 for VNZ/TEZ/D-IVA was inferior by >3.0 percentage points compared to ELX/TEZ/IVA. The null hypothesis was tested at a 1-sided significance level of 0.025.

With the exception of the populations, Studies 102 and 103 have the same estimand attributes. The primary effect of interest is the difference in the absolute change from ELX/TEZ/IVA baseline in ppFEV1 through Week 24 (averaging weeks 16 and 24) between VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups, regardless of whether patients used non-study drug CFTR modulators for more than 3 days or whether they discontinued treatment.

A supplemental estimand for the primary endpoint was defined similarly to the primary estimand, with the exception that intercurrent events were addressed using the hypothetical strategy, which targets the treatment effect that would have been obtained if patients had not used non-study drug CFTR modulators for more than 3 days and continued treatment as allocated. To assess added benefit resulting from treatment with VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA, key secondary endpoints were established that assessed efficacy in terms of restoration of CFTR function, which were tested for superiority.

The first key secondary efficacy endpoint was the absolute change from baseline in SwCl through Week 24.Other key secondary endpoints were the proportion of subjects with SwCl either <60 mmol/L or <30 mmol/L through Week 24. For these endpoints, data from Studies 102 and 103 were pooled to ensure sufficient power to test for superiority.

For the secondary endpoints, the same two intercurrent events were identified and only the treatment policy strategy to handle these intercurrent events was pre-specified. The treatment effects intended to be measured were 1) the difference in the absolute change from ELX/TEZ/IVA baseline in SwCl through Week 24 between VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups and 2) the Odds ratio comparing the response rates in VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups.

Sample size

Both studies were powered to demonstrate non-inferiority compared to ELX/TEZ/IVA for ppFEV1 (primary endpoint) and superiority for SwCl (key secondary endpoint).

For **Study 102**, assuming a within-group standard deviation (SD) of 8 and a 10% drop-out rate at Week 24 and a treatment difference of 0 between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, a sample size of 200 subjects in each group for a total of 400 subjects would have more than 90% power to test the primary hypothesis for the primary endpoint, based on a 1-sided, 2-sample t-test at a significance level of 0.025.

For the key secondary efficacy endpoint of absolute change from baseline in SwCl through Week 24, considering these assumptions, a sample size of 200 subjects in each treatment group would have more than 90% power to detect a difference between the treatment groups of -5 mmol/L, based on a 2-sided, 2-sample t-test at a significance level of 0.05.

Using the same assumptions for **Study 103**, a sample size of 275 subjects in each group for a total of 550 subjects would have more than 95% power to test the primary hypothesis for the primary endpoint and more than 95% power to detect a difference between the treatment groups of -5 mmol/L for the absolute change from baseline in SwCl through Week 24.

For the key secondary endpoints of the proportion of subjects with SwCl <60 mmol/L or <30 mmol/L, results of Studies 102 and 103 were pooled to ensure sufficient power for the analyses.

Statistical methods

For each Study 102 and 103, the **Full Analysis Set (FAS)** included all randomised subjects who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. The FAS was used to summarise subject demographics and baseline characteristics and for analyses of all efficacy endpoints in which subjects were analysed according to their randomised treatment group, unless otherwise specified.

The **Pooled Full Analysis Set (PFAS)** included all randomised subjects from Studies 102 and 103 who carried the intended CFTR mutation(s) and received at least 1 dose of study drug during the Treatment Period. The PFAS was used only for pooled analysis of selected endpoints.

The primary analysis was performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. The model included fixed categorical effects for treatment, visit, age at screening (<18 versus ≥18 years of age), genotype group (F/F, F/G, F/RF, TCR/non-F [Study 103 only]), and treatment-by-visit interaction, with baseline ppFEV1 and baseline SwCl as continuous covariates.

The key secondary endpoint of absolute change from baseline in SwCl through Week 24 was analysed based on an MMRM similar to the primary analysis of the primary efficacy endpoint.

The key secondary endpoints of response corresponding to SwCl <60 mmol/L or <30 mmol/L through Week 24 were analysed using a generalised estimating equations (GEE) model using the PFAS. The GEE model was used to estimate the odds ratio and included fixed categorical effects for treatment, age at screening (<18 vs ≥18 years), genotype group, visit, and treatment-by-visit interaction, with baseline ppFEV1 and baseline SwCl as continuous covariates. A logit link function and an unstructured working correlation matrix were specified.

**Results**

Participant flow and numbers analysed

*Study 102*

Of the 435 subjects enrolled in Study 102 (Figure 9), 37 (8.5%) subjects discontinued the study during the Run-in Period, 7 of whom were randomised and not dosed (and were therefore excluded from the FAS). In the Treatment Period, 398 subjects received at least 1 dose of study drug in the Treatment Period, 31 subjects (7.8%) discontinued treatment (15 [7.7%] in the VNZ/TEZ/D-IVA group and 16 [7.9%] in the ELX/TEZ/IVA group), and 23 subjects (5.8%) discontinued the study (12 [6.1%] in the VNZ/TEZ/D-IVA group and 11 [5.4%] in the ELX/TEZ/IVA group).

The main reasons for discontinuation of treatment were AE (14 subjects [3.5%] in total, of which 4 [2.0%] in the VNZ/TEZ/D-IVA group and 10 [5.0%] in the ELX/TEZ/IVA group) and refusal of further dosing (7 subjects [1.8%] in total, of which 5 [2.6%] in the VNZ/TEZ/D-IVA group and 2 [1.0%] in the ELX/TEZ/IVA group).

*Study 103*

Of the 597 subjects enrolled in Study 103 (Figure 10), 24 (4.0%) subjects discontinued the study during the Run-in Period. In the Treatment Period, 573 subjects received at least 1 dose of study drug, 41 subjects (7.2%) discontinued treatment (25 [8.8%] in the VNZ/TEZ/D-IVA group and 16 [5.5%] in the ELX/TEZ/IVA group), and 30 subjects (5.2%) discontinued the study (20 [7.0%] in the VNZ/TEZ/D-IVA group and 10 [3.5%] in the ELX/TEZ/IVA group).

The main reason for discontinuation of treatment was AE (23 subjects [4.0%] in total, of which 14 [4.9%] in the VNZ/TEZ/D-IVA group and 9 [3.1%] in the ELX/TEZ/IVA group).

**Figure 9. Participant flow Study 102**

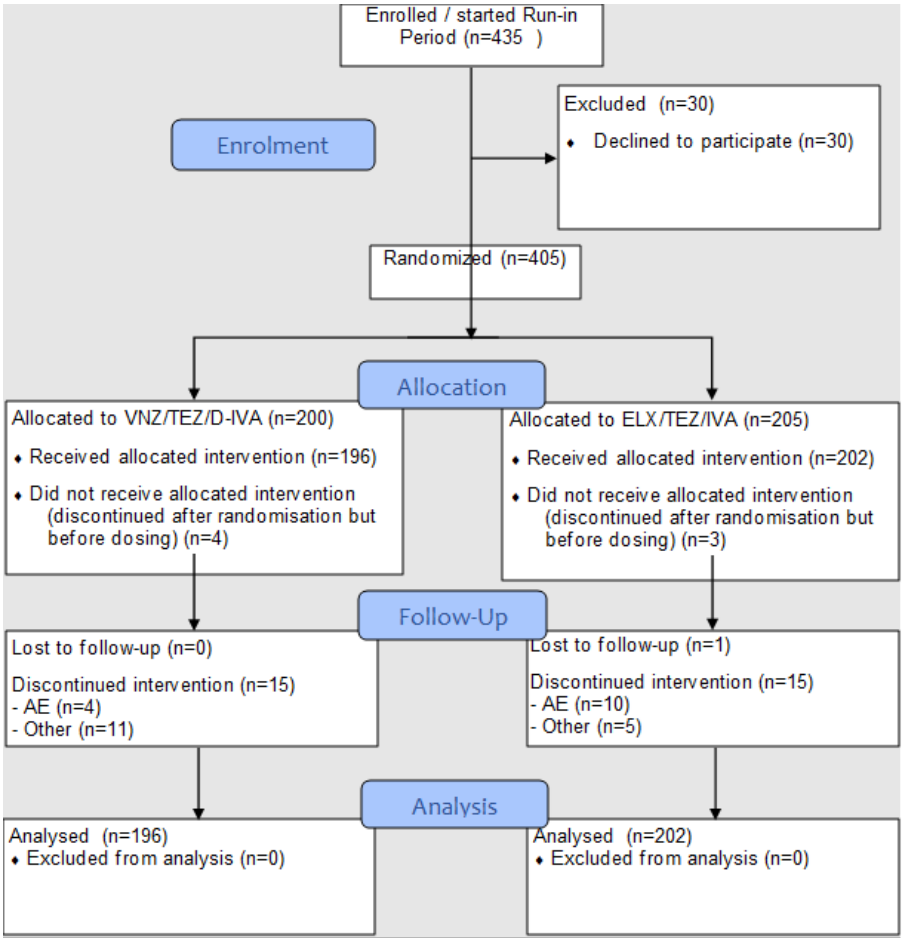
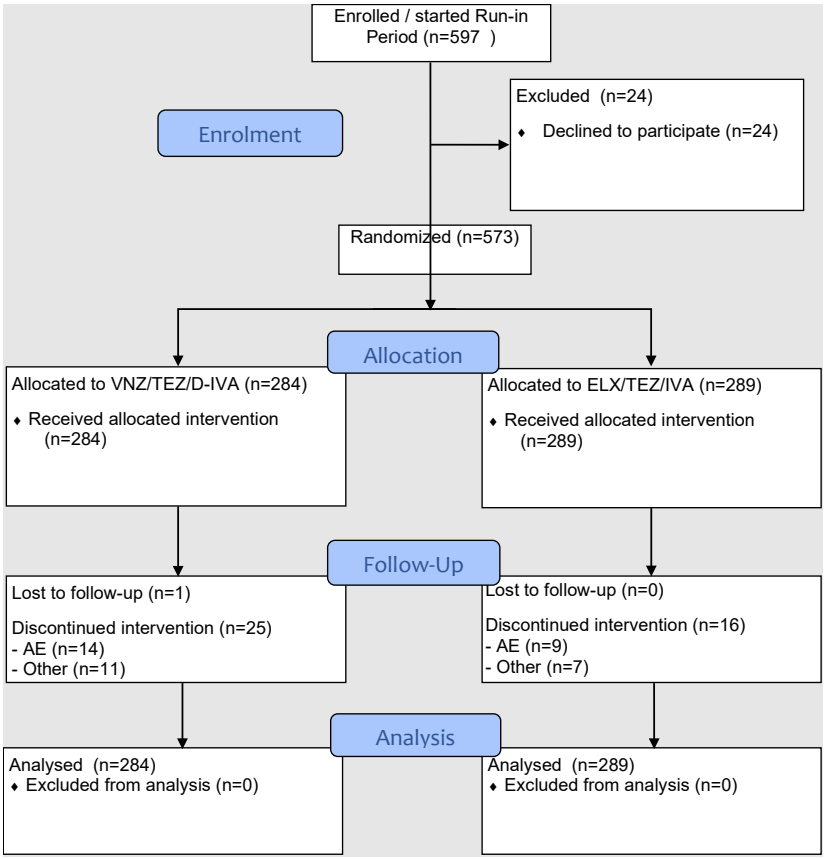


**Figure 10. Participant flow Study 103**




Recruitment

**Study 102** ran from 14 September 2021 (date first eligible subject signed the informed consent form) until 21 November 2023 (date last subject completed the last visit).

**Study 103** ran from 27 October 2021 (date first eligible subject signed the informed consent form) until 30 November 2023 (date last subject completed the last visit).

Conduct of the study

Protocol version 3.0 was implemented on 19 August 2021, prior to the start of enrolment. Substantial changes concerned:

- Increased planned sample size and Treatment Period duration;
- Liver function test elevations, CK elevations, rash, cataracts, hypoglycaemia, and neuropsychiatric events were designated as adverse events of special interest;
- Expanded study population to include subjects who have at least 1 CFTR mutation identified as responsive to ELX/TEZ/IVA based on *in vitro* data and no F508del mutation (Study 103 only).

No changes to the protocol were implemented after the start of enrolment.

Baseline data

*Demographic data*

Demographic data are provided in Table 15. Demographics were generally similar between treatment groups in both studies. In **Study 102**, the overall mean (SD) age of subjects at Day 1 was 30.8 (11.0) years, with 57 (14.3%) subjects being adolescents ≥12 to <18 years of age at Screening.

In **Study 103**, the overall mean (SD) age of subjects at Day 1 was 33.7 (12.5) years, with 79 (13.8%) subjects being adolescents ≥12 to <18 years of age at Screening.

**Table 15. Study 102 (F/MF subjects) and Study 103 (F/F, F/G, F/RF, TCR-non-F subjects): Subject demographics (FAS)**

| Characteristic | Study 102 | | Study 103 | |
|---|---|---|---|---|
| | ELX/TEZ/IVA N = 202 | VNZ/TEZ/D-IVA N = 196 | ELX/TEZ/IVA N = 289 | VNZ/TEZ/D-IVA N = 284 |
| **Age at Day 1 (years)** | | | | |
| n | 202 | 196 | 289 | 284 |
| Mean (SD) | 30.9 (11.4) | 30.8 (10.5) | 34.0 (12.4) | 33.3 (12.6) |
| Median | 31.3 | 30.3 | 33.8 | 32.6 |
| Min, max | 12.2, 71.6 | 12.4, 61.7 | 12.7, 63.4 | 12.2, 71.2 |
| **Age category at Screening Visit, n (%)** | | | | |
| ≥12 to <18 years | 31 (15.3) | 26 (13.3) | 38 (13.1) | 41 (14.4) |
| ≥18 years | 171 (84.7) | 170 (86.7) | 251 (86.9) | 243 (85.6) |
| **Sex, n (%)** | | | | |
| Male | 119 (58.9) | 116 (59.2) | 144 (49.8) | 149 (52.5) |
| Female | 83 (41.1) | 80 (40.8) | 145 (50.2) | 135 (47.5) |
| **Race, n (%)** | | | | |
| White | 197 (97.5) | 191 (97.4) | 262 (90.7) | 270 (95.1) |
| Black or African American | 1 (0.5) | 4 (2.0) | - | - |
| Asian | 0 | 1 (0.5) | 1 (0.3) | 1 (0.4) |
| Other | 1 (0.5) | 0 | 2 (0.7) | 1 (0.4) |
| More than 1 race | 3 (1.5) | 0 | 1 (0.3) | 2 (0.7) |
| Not collected per local regulations | - | - | 23 (8.0) | 10 (3.5) |
| **Geographic Region, n (%)[a]** | | | | |
| North America | 91 (45.0) | 87 (44.4) | 103 (35.6) | 114 (40.1) |
| Rest of World | 111 (55.0) | 109 (55.6) | 186 (64.4) | 170 (59.9) |

D-IVA: deutivacaftor; ELX: elexacaftor; F/F: homozygous for F508del; F/G: heterozygous for F508del and a gating mutation; F/MF: heterozygous for F508del and a minimal function mutation; F/RF: heterozygous for F508del and a residual function mutation; FAS: Full Analysis Set; IVA: ivacaftor; max: maximum value; min: minimum value; n: size of subsample; N: total sample size; TCR/non-F: heterozygous for a triple combination responsive mutation and no F508del mutation; TEZ: tezacaftor; VNZ: vanzacaftor

[a] North America included subjects from the United States and Canada (Study 103 only), and Rest of World included subjects from Europe, Israel, Australia, and New Zealand.

*Run-in Period*

An ELX/TEZ/IVA Run-in Period of 4 weeks was included to ensure a baseline on ELX/TEZ/IVA in all subjects. In **Study 102**, 86.7% of the randomised subjects were on commercial ELX/TEZ/IVA treatment on or prior to informed consent. In **Study 103**, this concerned 67.9% of the randomised subjects. As expected, ppFEV1, SwCl, and CFQ-R RD score in these CFTR modulator non-naïve subjects were maintained from the Screening Visit to baseline (Table 16). In subjects who were CFTR modulator naïve, clinically meaningful improvements in ppFEV1, SwCl, and CFQ-RD score were observed following open-label treatment with ELX/TEZ/IVA in the Run-in Period, consistent with the efficacy previously demonstrated in the Phase 3 pivotal studies of ELX/TEZ/IVA.

**Table 16. Study 102 (F/MF Subjects) and Study 103 (F/F, F/G, F/RF, TCR-non-F subjects): Change from screening to baseline after ELX/TEZ/IVA Run-in Period (FAS)**

| Parameter | Statistic | Study 102 | | Study 103 | |
|---|---|---|---|---|---|
| | | CFTRm Naïve N = 51 | CFTRm Non-naïve N = 347 | CFTRm Naïve N = 82 | CFTRm Non-naïve N = 491 |
| Change from screening to baseline in ppFEV1 (%) | n | 51 | 342 | 80 | 479 |
| | Mean (SD) | 14.4 (10.6) | -0.5 (5.0) | 11.7 (9.9) | 1.3 (6.0) |
| | Median | 12.5 | -0.5 | 9.7 | 0.5 |
| | Min, max | -2.4, 39.0 | -29.9, 21.3 | -4.8, 46.4 | -16.8, 37.1 |
| Change from screening to baseline in SwCl (mmol/L) | n | 50 | 332 | 78 | 480 |
| | Mean (SD) | -41.7 (15.1) | 0.3 (12.4) | -43.3 (19.4) | -6.6 (20.0) |
| | Median | -44.0 | 1.3 | -44.9 | -0.3 |
| | Min, max | -69.0, -8.3 | -80.5, 51.0 | -83.8, 3.5 | -71.0, 43.8 |
| Change from screening to baseline in CFQ-R RD score (points) | n | 51 | 337 | 82 | 478 |
| | Mean (SD) | 25.7 (20.6) | -0.2 (13.1) | 23.0 (18.4) | 3.4 (14.9) |
| | Median | 22.2 | 0.0 | 22.2 | 0.0 |
| | Min, max | -8.3, 66.7 | -72.2, 50.0 | -16.7, 72.2 | -44.4, 66.7 |

CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; CFTRm: CFTR modulator; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for F508del; F/G: heterozygous for F508del and a gating mutation; F/MF: heterozygous for F508del and a minimal function mutation; F/RF: heterozygous for F508del and a residual function mutation; IVA: ivacaftor: n: size of subsample; N: total sample size; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR/non-F: heterozygous for a triple combination responsive mutation and no F508del mutation; TEZ: tezacaftor

Note: Prior CFTR modulator use included the most recent CFTR modulator on or prior to informed consent for each subject.

*Baseline characteristics*

Baseline characteristics are provided in Table 17. In both studies, baseline characteristics were generally similar between treatment groups. The baseline characteristics reflect the improved CFTR function derived from treatment with ELX/TEZ/IVA. Mean SwCl levels at baseline (after 4-week ELX/TEZ/IVA treatment) were approximately 10 mmol/L lower in subjects in Study 103 compared to those in Study 102.

**Table 17. Study 102 (F/MF Subjects) and Study 103 (F/F, F/G, F/RF, TCR-non-F subjects): Subjects baseline characteristics (FAS)**

| Characteristic | Study 102 | | Study 103 | |
|---|---|---|---|---|
| | ELX/TEZ/IVA N = 202 | VNZ/TEZ/D-IVA N = 196 | ELX/TEZ/IVA N = 289 | VNZ/TEZ/D-IVA N = 284 |
| **Genotype group, n (%)** | | | | |
| F/MF | 202 (100) | 196 (100) | 0 | 0 |
| F/F | 0 | 0 | 224 (77.5) | 222 (78.2) |
| F/G | 0 | 0 | 20 (6.9) | 19 (6.7) |
| F/RF | 0 | 0 | 23 (8.0) | 23 (8.1) |
| TCR/non-F | 0 | 0 | 22 (7.6) | 20 (7.0) |
| **Weight (kg)** | | | | |
| Mean (SD) | 64.54 (13.75) | 65.08 (13.32) | 65.05 (13.35) | 66.58 (13.98) |
| **BMI (kg/m2)** | | | | |
| Mean (SD) | 23.03 (3.85) | 22.71 (3.40) | 22.92 (3.27) | 23.27 (4.02) |
| **ppFEV1 category at Day -14[a], n (%)** | | | | |
| <70 percentage points | 106 (52.5) | 105 (53.6) | 166 (57.4) | 161 (56.7) |
| ≥70 percentage points | 96 (47.5) | 91 (46.4) | 123 (42.6) | 123 (43.3) |
| **ppFEV1 (%) at baseline, n (%)** | | | | |
| Mean (SD) | 67.2 (14.6) | 67.0 (15.3) | 66.4 (14.9) | 67.2 (14.6) |
| **ppFEV1 category at baseline, n (%)** | | | | |
| <40 percentage points | 3 (1.5) | 6 (3.1) | 7 (2.4) | 5 (1.8) |
| ≥40 to <70 percentage points | 111 (55.0) | 95 (48.5) | 160 (55.4) | 149 (52.5) |

| | | | | |
|---|---|---|---|---|
| ≥70 to ≤90 percentage points | 79 (39.1) | 85 (43.4) | 107 (37.0) | 112 (39.4) |
| >90 percentage points | 8 (4.0) | 7 (3.6) | 12 (4.2) | 13 (4.6) |
| Missing | 1 (0.5) | 3 (1.5) | 3 (1.0) | 5 (1.8) |
| **SwCl (mmol/L) at baseline** | | | | |
| Mean (SD) | 54.3 (18.2) | 53.6 (17.0) | 42.1 (17.9) | 43.4 (18.5) |
| **SwCl category at baseline, n (%)** | | | | |
| <30 mmol/L | 19 (9.4) | 17 (8.7) | 80 (27.7) | 72 (25.4) |
| ≥30 to <60 mmol/L | 105 (52.0) | 114 (58.2) | 154 (53.3) | 158 (55.6) |
| ≥60 mmol/L | 77 (38.1) | 63 (32.1) | 48 (16.6) | 52 (18.3) |
| Missing | 1 (0.5) | 2 (1.0) | 7 (2.4) | 2 (0.7) |
| **CFQ-R RD (points) at baseline** | | | | |
| Mean (SD) | 82.9 (15.7) | 85.8 (14.7) | 85.6 (13.2) | 85.7 (13.2) |

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; D-IVA: deutivacaftor; ELX: elexacaftor; F/F: homozygous for F508del; F/G: heterozygous for F508del and a gating mutation; F/MF: heterozygous for F508del and a minimal function mutation; F/RF: heterozygous for F508del and a residual function mutation; FAS: Full Analysis Set; IVA: ivacaftor; max: maximum value; min: minimum value; n: size of subsample; N: total sample size; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR/non-F: heterozygous for a triple combination responsive mutation and no F508del mutation; TEZ: tezacaftor; VNZ: vanzacaftor

[a] If the Day -14 value was not valid or was not available, the most recent available clinic-assessed value was used.

Intercurrent events

The number of subjects meeting intercurrent events criteria (discontinued treatment before Week 24; received a non-study CFTR modulator for >3 days during either the Run-in Period or prior to Week 24 of the Treatment Period) are provided by treatment group for Study 102 and Study 103, respectively in Table 18. The reason for treatment discontinuation and the CFTR modulator used are also provided.

**Table 18. Study 102 (F/MF Subjects) and Study 103 (F/F, F/G, F/RF, TCR-non-F subjects): Subjects meeting intercurrent events criteria**

| | Study 102 | | Study 103 | |
|---|---|---|---|---|
| | ELX/TEZ/IVA N = 202 n (%) | VNZ/TEZ/D-IVA N = 196 n (%) | ELX/TEZ/IVA N = 289 n (%) | VNZ/TEZ/D-IVA N = 284 n (%) |
| **Subjects meeting any ICE criteria** | 8 (4.0) | 8 (4.1) | 11 (3.8) | 19 (6.7) |
| **Treatment discontinuation** | 8 (4.0) | 7 (3.6) | 10 (3.5) | 17 (6.0) |
| AE | 7 (3.5) | 1 (0.5) | 5 (1.7) | 11 (3.9) |
| Subject refused further dosing (not due to AE) | 0 | 4 (2.0) | 0 | 2 (0.7) |
| Commercial drug is available for subject | | | 0 | 1 (0.4) |
| Non-compliance with study drug | | | 1 (0.3) | 1 (0.4) |
| Pregnancy (self or partner) | 0 | 2 (1.0) | 2 (0.7) | 1 (0.4) |
| Other | 1 (0.5) | 0 | 2 (0.7) | 2 (0.7) |
| **CFTR modulator use** | 4 (2.0) | 5 (2.6) | 6 (2.1) | 7 (2.5) |
| Orkambi | | | 1 (0.3) | 1 (0.4) |
| Symdeko/Symkevi | | | 1 (0.3) | 0 |
| Trikafta/Kaftrio | 4 (2.0) | 5 (2.6) | 4 (1.4) | 6 (2.1) |

AE: adverse event; D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; ICE: intercurrent event(s); IVA: ivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor

Note: Full Analysis Set included all randomised subjects who carried the intended *CFTR* mutation(s) and received at least 1 dose of study drug during the Treatment Period. Treatment discontinuation = treatment discontinuation prior to Week 24.

CFTR modulator use = use of non-study drug CFTR modulators for >3 days in either the Run-in Period or the Treatment Period prior to Week 24. When different treatment discontinuation reasons were selected for VNZ/TEZ/D-IVA, ELX/TEZ/IVA, and IVA, reasons were reported in each of the corresponding categories.

Missing data patterns

The (monotone) missing data patterns, by recorded intercurrent event are presented for study 102 and 103 in Table 19. Most of the subjects with missing data by week 24 had no recorded intercurrent event. Subjects are only represented once in the Table 19, at the first timepoint where missing data were noted.

**Table 19. Study 102 (F/MF Subjects) and Study 103 (F/F, F/G, F/RF, TCR-non-F subjects): Missing Data for ppFEV$_1$ Up to Week 24 Among Subjects With and Without ICE Through Week 24**

| Study 102 | | | | | | |
|---|---|---|---|---|---|---|
| | **N** | **Day 15** | **Week 4** | **Week 8** | **Week 16** | **Week 24** |
| **Subjects with no ICE** | | | | | | |
| ELX/TEZ/IVA | 194 | 1 (0.5) | 0 | 0 | 2 (1.0) | 5 (2.6) |
| VNZ/TEZ/D-IVA | 188 | 0 | 0 | 0 | 2 (1.1) | 7 (3.7) |
| **ICE: Treatment discontinuation prior to Week 24[a]** | | | | | | |
| **Overall** | n | | | | | |
| ELX/TEZ/IVA | 8 | 0 | 1 (12.5) | 1 (12.5) | 2 (25.0) | 1 (12.5) |
| VNZ/TEZ/D-IVA | 6 | 0 | 0 | 0 | 2 (33.3) | 1 (16.7) |
| **ICE: CFTR modulator use prior to Week 24[a]** | | | | | | |
| **Overall** | n | | | | | |
| ELX/TEZ/IVA | 0 | -- | -- | -- | -- | -- |
| VNZ/TEZ/D-IVA | 2 | 0 | 0 | 0 | 0 | 0 |

| Study 103 | | | | | | |
|---|---|---|---|---|---|---|
| | **N** | **Day 15** | **Week 4** | **Week 8** | **Week 16** | **Week 24** |
| **Subjects with no ICE** | | | | | | |
| ELX/TEZ/IVA | 278 | 0 | 0 | 0 | 1 (0.4) | 7 (2.5) |
| VNZ/TEZ/D-IVA | 265 | 0 | 0 | 1 (0.4) | 2 (0.8) | 7 (2.6) |
| **ICE: Treatment discontinuation prior to Week 24[a]** | | | | | | |
| **Overall** | n | | | | | |
| ELX/TEZ/IVA | 9 | 0 | 0 | 0 | 1 (11.1) | 2 (22.2) |
| VNZ/TEZ/D-IVA | 16 | 0 | 0 | 2 (12.5) | 3 (18.8) | 4 (25.0) |
| **ICE: CFTR modulator use prior to Week 24[a]** | | | | | | |
| **Overall** | n | | | | | |
| ELX/TEZ/IVA | 2 | 0 | 0 | 1 (50.0) | 0 | 0 |
| VNZ/TEZ/D-IVA | 3 | 0 | 0 | 0 | 1 (33.3) | 0 |

D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; ICE: intercurrent event(s);

IVA: ivacaftor; N: number of subjects in the category; n: number of subjects in the category with monotone missing ppFEV$_1$ starting at the visit; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; VNZ: vanzacaftor

Note: Full Analysis Set included all randomised subjects who carried the intended *CFTR* mutation(s) and received at least 1 dose of study drug during the Treatment Period. Percentage is n/N. Treatment discontinuation = treatment discontinuation prior to Week 24. CFTR modulator use = use of non-study drug CFTR modulators >3 days in either the Run-in Period or the Treatment Period prior to Week 24.

[a] Subjects experiencing both ICE are displayed under the ICE that occurred earlier. If both ICE occurred at the same time, the subject is displayed under treatment discontinuation prior to Week 24.

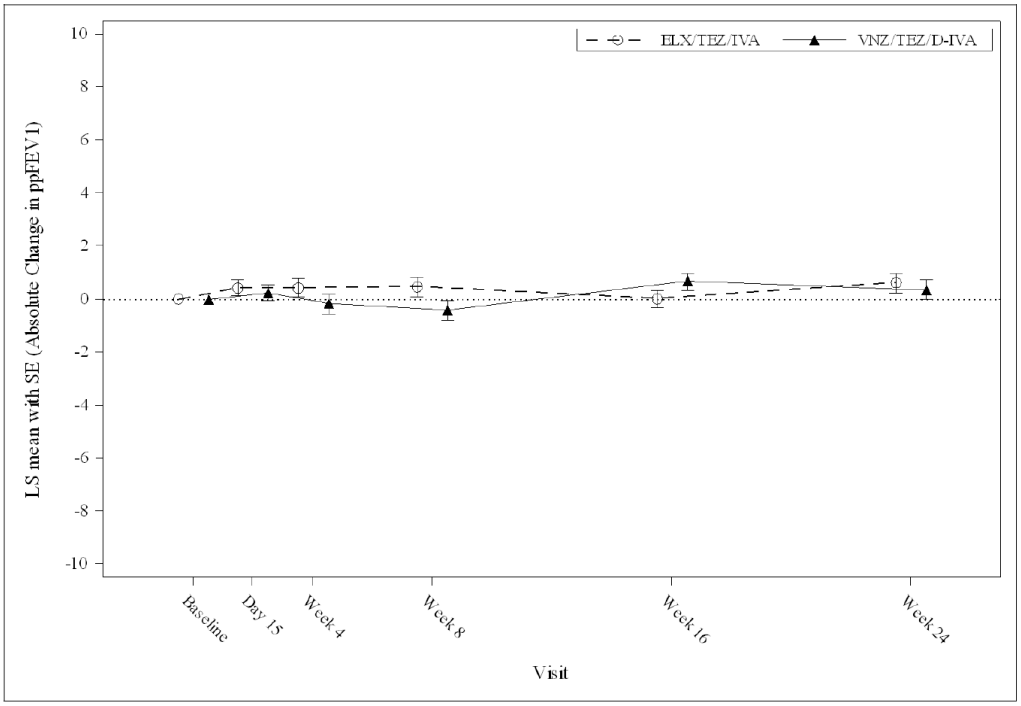
Outcomes and estimation

*Primary endpoint: Absolute change from baseline in ppFEV1 through Week 24*

In **Study 102**, from a baseline established on ELX/TEZ/IVA in the Run-in Period, treatment with VNZ/TEZ/D-IVA was non-inferior to ELX/TEZ/IVA in absolute change from baseline in ppFEV1 through Week 24, with a least squares (LS) mean treatment difference of 0.2 percentage points (95% CI: -0.7, 1.1) between VNZ/TEZ/D-IVA and ELX/TEZ/IVA (Table 20, Figure 11).

In **Study 103**, the LS mean treatment difference was 0.2 percentage points (95% CI: -0.5, 0.9) (Table 20 and Figure 12).

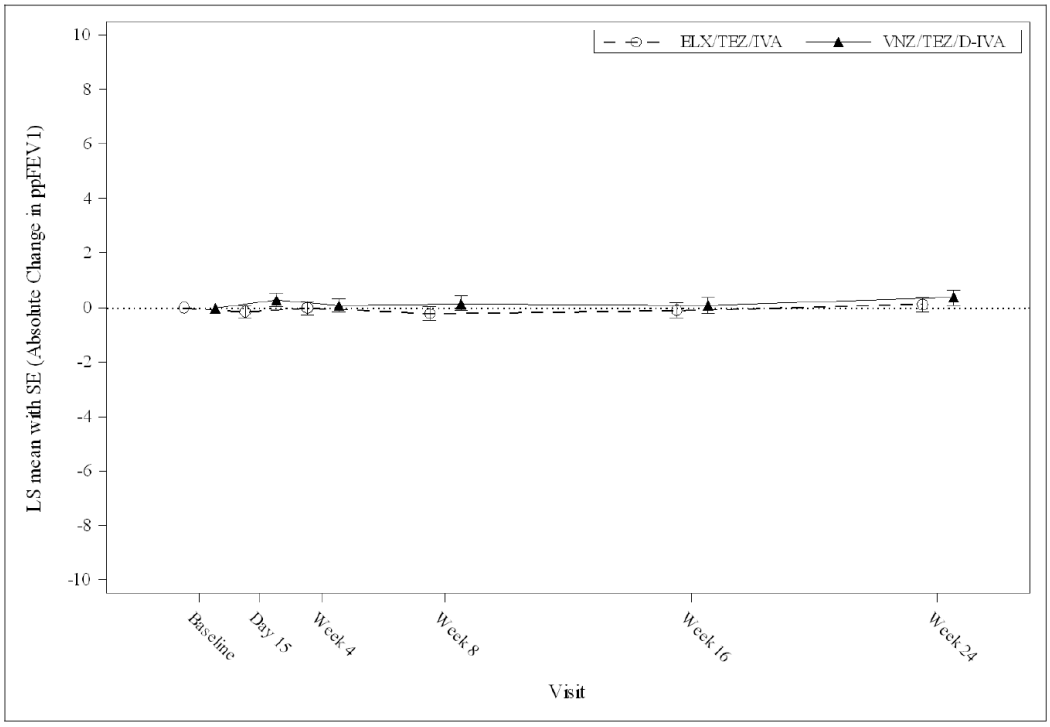
**Figure 11. Study 102 (F/MF Subjects): Following a 4-Week Run-in With ELX/TEZ/IVA to Establish Baseline, MMRM Analysis of Absolute Change From Baseline in ppFEV1 (Percentage Points) at Each Visit up to Week 24 (FAS)**




D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/MF: heterozygous for *F508del* and a minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: MMRM included data from all available visits up to Week 24. The model included fixed categorical effects for treatment, visit, age at screening (<18 vs ⩾18 years), and treatment-by-visit interaction, with baseline ppFEV1 and baseline SwCl as continuous covariates. An unstructured covariance structure was used. A Kenward-Roger approximation was used for denominator degrees of freedom.

**Figure 12. Study 103 (F/F, F/G, F/RF, and TCR-non-F Subjects): Following a 4-Week Run-in With ELX/TEZ/IVA to Establish Baseline, MMRM Analysis of Absolute Change From Baseline in ppFEV1 (Percentage Points) at Each Visit up to Week 24 (FAS)**




D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/G: heterozygous for *F508del* and a gating mutation; F/RF: heterozygous for *F508del* and a residual function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR/non-F: heterozygous for a triple combination responsive mutation and no *F508del* mutation; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: MMRM included data from all available visits up to Week 24. The model included fixed categorical effects for treatment, visit, age at screening (<18 vs ⩾18 years), genotype group, and treatment-by-visit interaction, with baseline ppFEV1 and baseline SwCl as continuous covariates. An unstructured covariance structure was used. A Kenward-Roger approximation was used for denominator degrees of freedom.

**Table 20. Study 102 (F/MF Subjects) and Study 103 (F/F, F/G, F/RF, TCR-non-F subjects):**

**Primary and Key Secondary Efficacy Analyses (FAS and PFAS)**

| | | Study 102 | | Study 103 | |
|---|---|---|---|---|---|
| **Analysis** | **Statistic** | ELX/TEZ/IVA N = 202 (FAS) | VNZ/TEZ/D-IVA N = 196 (FAS) | ELX/TEZ/IVA N = 289 (FAS) | VNZ/TEZ/D-IVA N = 284 (FAS) |
| **Primary Endpoint** | | | | | |
| Absolute change from baseline in ppFEV1 through Week 24 (%) (FAS) | n | 193 | 187 | 276 | 268 |
| | LS mean (SE) | 0.3 (0.3) | 0.5 (0.3) | 0.0 (0.2) | 0.2 (0.3) |
| | 95% CI of LS mean | -0.3, 0.9 | -0.1, 1.1 | -0.5, 0.5 | -0.3, 0.7 |
| | **LS mean difference (95% CI)** | -- | **0.2 (-0.7, 1.1)** | -- | **0.2 (-0.5, 0.9)** |
| | P value[a] | -- | <0.0001 | -- | <0.0001 |
| **Key Secondary Endpoints** | | | | | |
| Absolute change from baseline in SwCl through Week 24 (mmol/L) (FAS) | n | 194 | 185 | 276 | 270 |
| | LS mean (SE) | 0.9 (0.8) | -7.5 (0.8) | -2.3 (0.7) | -5.1 (0.7) |
| | 95% CI of LS mean | -0.6, 2.3 | -9.0, -6.0 | -3.6, -0.9 | -6.4, -3.7 |
| | **LS mean difference (95% CI)** | -- | **-8.4 (-10.5, -6.3)** | -- | **-2.8 (-4.7, -0.9)** |

| | | | | | |
|---|---|---|---|---|---|
| | P value[b] | -- | <0.0001 | -- | 0.0034 |
| | | **Studies 102 and 103 pooled** | | | |
| | | ELX/TEZ/IVA N = 491 (PFAS) | VNZ/TEZ/D-IVA N = 480 (PFAS) | | |
| Proportion of subjects with SwCl <60 mmol/L through Week 24 (PFAS) | n/N1 | 367/479 | 399/465 | | |
| | Proportion (%) | 76.6 | 85.8 | | |
| | **Estimated odds ratio (95% CI)** | -- | **2.21 (1.55, 3.15)** | | |
| | P value[b] | -- | <0.0001 | | |
| Proportion of subjects with SwCl <30 mmol/L through Week 24 (PFAS) | n/N1 | 108/479 | 142/465 | | |
| | Proportion (%) | 22.5 | 30.5 | | |
| | **Estimated odds ratio (95% CI)** | -- | **2.87 (2.00, 4.12)** | | |
| | P value[b] | -- | <0.0001 | | |

D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for F508del; F/G: heterozygous for F508del and a gating mutation; F/MF: heterozygous for F508del and a minimal function mutation; F/RF: heterozygous for F508del and a residual function mutation; IVA: ivacaftor: LS: least squares; n: size of subsample; N: total sample size; N1: number of subjects with non-missing SwCl at Week 16 or Week 24; P: probability; PFAS: Pooled Full Analysis Set; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR/non-F: heterozygous for a triple combination responsive mutation and no F508del mutation; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: Analyses were based on the FAS unless noted otherwise. FAS was defined as all randomised subjects who carry the intended CFTR allele mutation and received at least 1 dose of study drug during the Treatment Period. PFAS was defined as the pooled FAS from Studies 102 and 103.

[a] 1-sided P value for non-inferiority versus ELX/TEZ/IVA

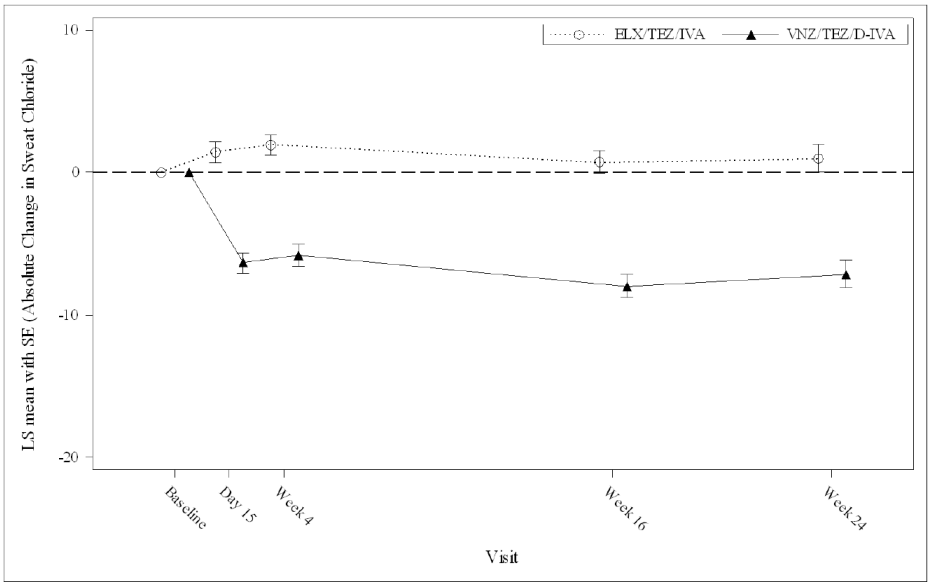
[b] 2-sided P value for superiority versus ELX/TEZ/IVA

*Key secondary endpoint: Absolute change from baseline in SwCl through Week 24*

In **Study 102**, from a baseline established on ELX/TEZ/IVA in the Run-in Period, treatment with VNZ/TEZ/D-IVA resulted in a greater reduction in SwCl from baseline through Week 24 compared to ELX/TEZ/IVA, with an LS mean treatment difference of -8.4 mmol/L (95% CI: -10.5, -6.3) (Figure 13, Table 20).

In **Study 103**, the LS mean treatment difference was -2.8 mmol/L (95% CI: -4.7, -0.9) (Figure 14, Table 20).

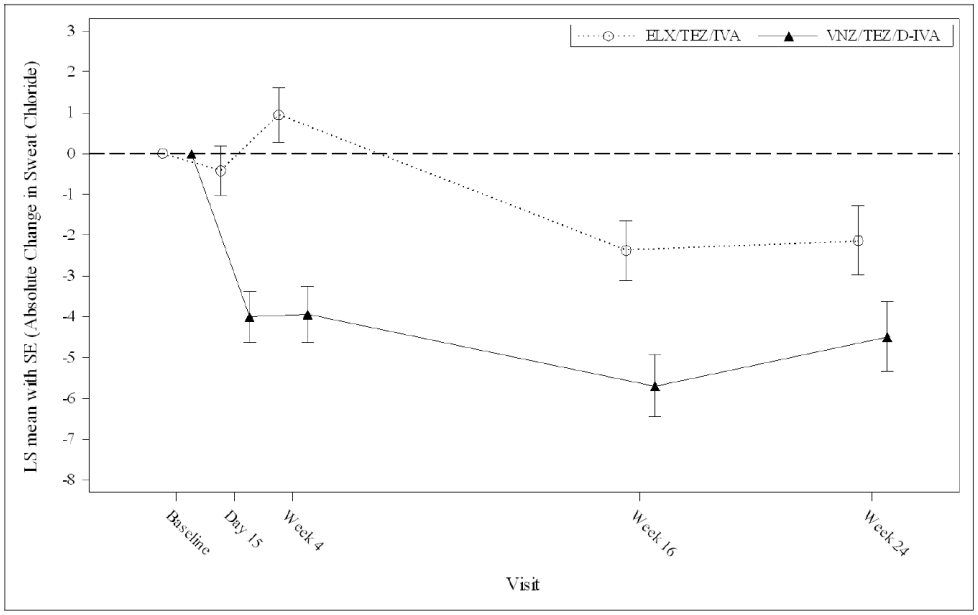
**Figure 13. Study 102 (F/MF Subjects): Following a 4-Week Run-in With ELX/TEZ/IVA to Establish Baseline, MMRM Analysis of Absolute Change From Baseline in SwCl mmol/L at Each Visit up to Week 24 (FAS)**



D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/MF: heterozygous for *F508del* and a minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: MMRM included data from all available visits up to Week 24. The model included fixed categorical effects for treatment, visit, age at screening (<18 vs ⩾18 years), genotype group, and treatment-by-visit interaction, with baseline ppFEV1 and baseline SwCl as continuous covariates. An unstructured covariance structure was used. A Kenward-Roger approximation was used for denominator degrees of freedom.

**Figure 14. Study 103 (F/F, F/G, F/RF, and TCR-non-F Subjects): Following a 4-Week Run-in With ELX/TEZ/IVA to Establish Baseline, MMRM Analysis of Absolute Change From Baseline in SwCl mmol/L at Each Visit up to Week 24 (FAS)**




D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/G: heterozygous for *F508del* and a gating mutation; F/RF: heterozygous for *F508del* and a residual function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR/non-F: heterozygous for a triple combination responsive mutation and no *F508del* mutation; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: MMRM included data from all available visits up to Week 24. The model included fixed categorical effects for treatment, visit, age at screening (<18 vs ⩾18 years), genotype group, and treatment-by-visit interaction, with baseline ppFEV1 and baseline SwCl as continuous covariates. An unstructured covariance structure was used. A Kenward-Roger approximation was used for denominator degrees of freedom.

*Key secondary endpoints: Proportion of subjects with SwCl <60 mmol/L or <30 mmol/L through Week 24 (pooled between Studies 102 and 103)*

Based on pooled data from Studies 102 and 103, the estimated odds ratio for the proportion of subjects with SwCl <60 mmol/L through week 24 was 2.21 (95% CI: 1.55, 3.15). The estimated odds ratio for the proportion of subjects with SwCl <30 mmol/L through Week 24 was 2.87 (95% CI: 2.00, 4.12) (Table 20).

*Other secondary endpoints*

Treatment with VNZ/TEZ/D-IVA resulted in similar rates of PEx through Week 52 compared to ELX/TEZ/IVA.

In **Study 102** (F/MF subjects), the PEx rate difference was -0.10 (95% CI: -0.24, 0.04).

In **Study 103** (F/F, F/G, F/R, TCR/non-F subjects), the PEx rate difference was 0.03 (95% CI: -0.07, 0.13) (Table 21).

Treatment with VNZ/TEZ/D-IVA resulted in similar values in absolute change from baseline in CFQ-R RD score through Week 24 compared to ELX/TEZ/IVA, with an LS mean treatment difference of 2.3 points (95% CI: -0.6, 5.2) in **Study 102** and -0.1 points (95% CI: -2.3, 2.1) in **Study 103** (Table 21).

Treatment with VNZ/TEZ/D-IVA resulted in similar values in absolute change from baseline in ppFEV1 through Week 52 compared to ELX/TEZ/IVA, with an LS mean treatment difference of 0.1 percentage points (95% CI: -0.8, 1.0) in **Study 102** and 0.3 percentage points (95% CI: -0.4, 1.0) in **Study 103** (Table 2**1**). ppFEV1 values through Week 52 were consistent with values through Week 24 in both studies.

Treatment with VNZ/TEZ/D-IVA resulted in reductions in SwCl through Week 52 compared to ELX/TEZ/IVA, with an LS mean treatment difference of -8.0 mmol/L (95% CI: -9.9, -6.1) in **Study 102** and -2.8 mmol/L (95% CI: -4.6, -1.0) in **Study 103** (Table 21). SwCl values through Week 52 were consistent with values through Week 24.

In **Study 102**, the estimated odds ratio for the proportion of subjects with SwCl <60 mmol/L through Week 24 was 4.28 (95% CI: 2.57, 7.11). The estimated odds ratio for the proportion of subjects with SwCl <30 mmol/L through Week 24 was 7.19 (95% CI: 3.54, 14.59).

In **Study 103**, the estimated odds ratios for the proportion of subjects with SwCl <60 mmol/L through Week 24 was 1.10 (95% CI: 0.65, 1.87). The estimated odds ratio for the proportion of subjects with SwCl <30 mmol/L through Week 24 was 2.06 (95% CI: 1.33, 3.18) (Table 21).

Results are consistent with the pooled analyses in favouring VNZ/TEZ/D-IVA treatment.

**Table 21. Study 102 (F/MF Subjects) and Study 103 (F/F, F/G, F/RF, TCR-non-F subjects): secondary efficacy analyses (FAS)**

| Analysis | Statistic | Study 102 | | Study 103 | |
|---|---|---|---|---|---|
| | | ELX/TEZ/IVA N = 202 (FAS) | VNZ/TEZ/D-IVA N = 196 (FAS) | ELX/TEZ/IVA N = 289 (FAS) | VNZ/TEZ/D-IVA N = 284 (FAS) |
| Number of PEx through Week 52 (FAS) | Number of subjects with events, n (%) | 60 (29.7) | 50 (25.5) | 59 (20.4) | 61 (21.5) |
| | Number of events | 90 | 67 | 79 | 86 |
| | Event rate per year | 0.42 | 0.32 | 0.26 | 0.29 |
| | **Rate difference (95% CI)** | -- | **-0.10 (-0.24, 0.04)** | -- | **0.03 (-0.07, 0.13)** |
| Absolute change from baseline in CFQ-R RD score through Week 24 (points) (FAS) | n | 192 | 186 | 270 | 268 |
| | LS mean (SE) | -1.7 (1.0) | 0.5 (1.1) | -1.2 (0.8) | -1.2 (0.8) |
| | 95% CI of LS mean | -3.8, 0.3 | -1.5, 2.6 | -2.7, 0.4 | -2.8, 0.3 |
| | **LS mean difference (95% CI)** | -- | **2.3 (-0.6, 5.2)** | -- | **-0.1 (-2.3, 2.1)** |
| Absolute change from baseline in ppFEV1 through Week 52 (percentage points) (FAS) | n | 196 | 189 | 277 | 271 |
| | LS mean (SE) | 0.4 (0.3) | 0.5 (0.3) | 0.0 (0.2) | 0.3 (0.2) |
| | 95% CI of LS mean | -0.3, 1.0 | -0.1, 1.1 | -0.5, 0.5 | -0.2, 0.8 |
| | **LS mean difference (95% CI)** | -- | **0.1 (-0.8, 1.0)** | -- | **0.3 (-0.4, 1.0)** |
| Absolute change from baseline in SwCl through Week 52 (mmol/L) (FAS) | n | 195 | 188 | 277 | 271 |
| | LS mean (SE) | 0.5 (0.7) | -7.5 (0.7) | -2.2 (0.6) | -5.0 (0.6) |
| | 95% CI of LS mean | -0.8, 1.8 | -8.9, -6.2 | -3.5, -1.0 | -6.2, -3.7 |
| | **LS mean difference (95% CI)** | -- | **-8.0 (-9.9, -6.1)** | -- | **-2.8 (-4.6, -1.0)** |
| Proportion of subjects with SwCl <60 mmol/L through Week 24 (FAS) | n/N1 | 116/196 | 153/190 | 251/283 | 246/275 |
| | Proportion (%) | 59.2 | 80.5 | 88.7 | 89.5 |
| | **Estimated odds ratio (95% CI)** | -- | **4.28 (2.57, 7.11)** | -- | **1.10 (0.65, 1.87)** |
| Proportion of subjects with SwCl <30 mmol/L through Week 24 (FAS) | n/N1 | 13/196 | 37/190 | 95/283 | 105/275 |
| | Proportion (%) | 6.6 | 19.5 | 33.6 | 38.2 |
| | **Estimated odds ratio (95% CI)** | -- | **7.19 (3.54, 14.59)** | -- | **2.06 (1.33, 3.18)** |

CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for F508del; F/G: heterozygous for F508del and a gating mutation; F/MF: heterozygous for F508del and a minimal function mutation; F/RF: heterozygous for F508del and a residual function mutation; IVA: ivacaftor: LS: least squares; n: size of subsample; N: total sample size; N1: number of subjects with non-missing SwCl at Week 16 or Week 24; PEx: pulmonary exacerbation; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR/non-F: heterozygous for a triple combination responsive mutation and no F508del mutation; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: Analyses were based on the FAS unless noted otherwise. FAS was defined as all randomised subjects who carry the intended CFTR allele mutation and received at least 1 dose of study drug during the Treatment Period.

Ancillary analyses

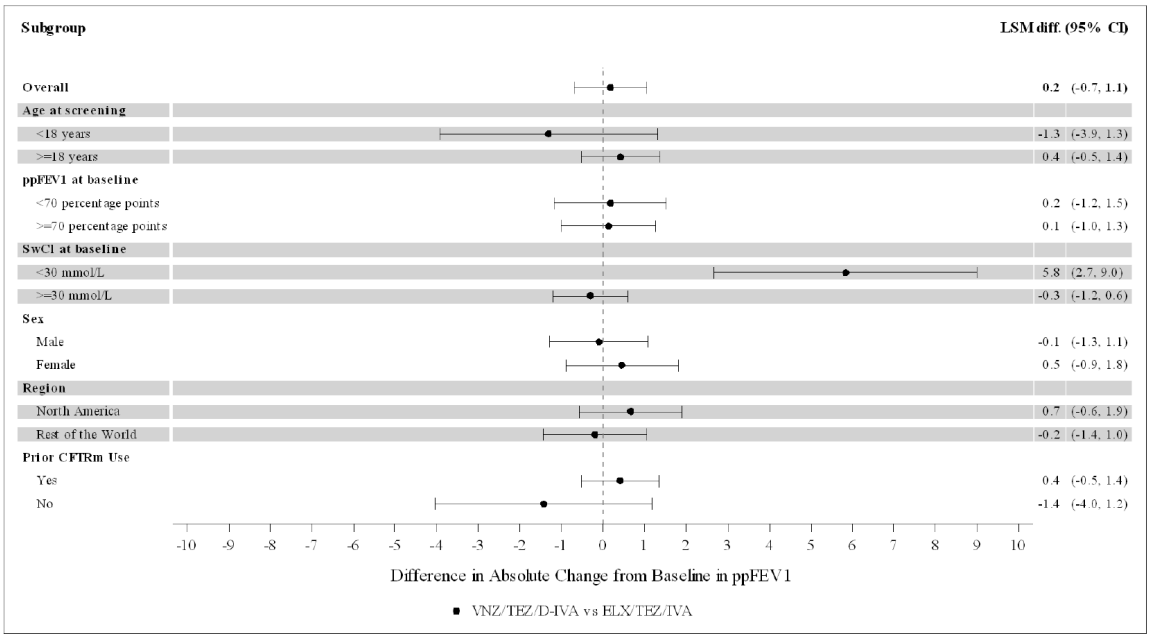
*Subgroup analyses for the primary endpoint*

Prespecified subgroup analyses of the primary efficacy endpoint were performed in a manner similar to that of the primary analysis in Studies 102 and 103.

The results of each subgroup analysis were consistent with the result from the primary analysis, namely, that regardless of differences in age, ppFEV1 at baseline, SwCl at baseline, sex, and geographic region, subjects in the VNZ/TEZ/D-IVA group had similar improvements in ppFEV1 compared to subjects in the ELX/TEZ/IVA group in Study 102 (Figure 15) and Study 103 (Figure 16), respectively.

In Study 103, an ad hoc subgroup analysis was performed by genotype group (F/F, F/RF, F/G, TCR/non-F) to demonstrate the efficacy of VNZ/TEZ/D-IVA in a population with at least one *in vitro* responsive allele but without an F508del allele. The results in the genotype subgroups were consistent with the result from the primary analysis. The smaller sample sizes and large within-group heterogeneity for some of the genotype groups are reflected in larger uncertainty (95% CI) (Figure 15).

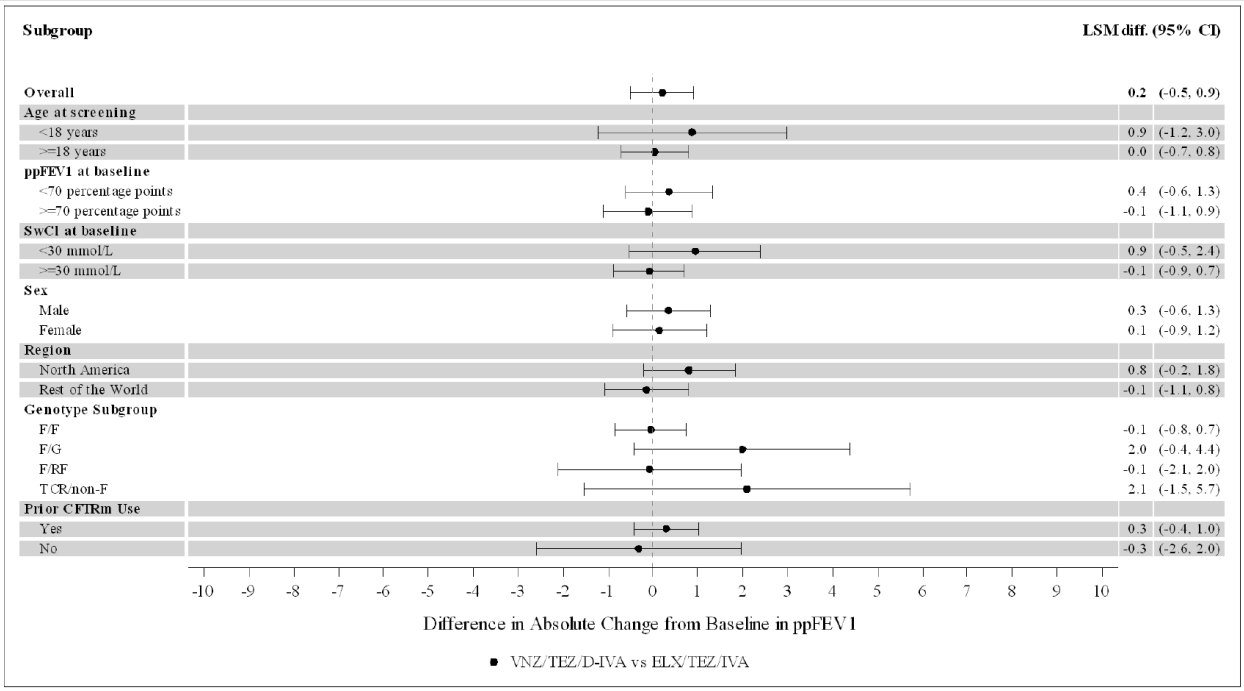
**Figure 15. Forest plot of LS mean difference between treatments with 95% CI for absolute change from baseline in ppFEV1 (percentage points) through week 24 by subgroup (Study 102, FAS)**




CFTRm: CFTR modulator; D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: Treatment effect through Week 24 is estimated by averaging Weeks 16 and 24.

**Figure 16. Forest plot of LS mean difference between treatments with 95% CI for absolute change from baseline in ppFEV1 (percentage points) through week 24 by subgroup (Study 103, FAS)**




CFTRm: CFTR modulator; D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/G: heterozygous for *F508del* and a gating mutation; F/RF: heterozygous for *F508del* and a residual function mutation; IVA: ivacaftor; LS: least squares; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR/non-F: heterozygous for a triple combination responsive mutation and no *F508del* mutation; TEZ: tezacaftor; VNZ: vanzacaftor

Note: Treatment effect through Week 24 is estimated by averaging Weeks 16 and 24.

*Additional analyses for the primary and key secondary endpoints*

**Table 22. Summary of status beyond week 24 visit for subjects with monotone missing data up to week 24 (full analysis set*)***

| | ppFEV$_1$ | | SwCl | |
|---|---|---|---|---|
| | **Study 102 N = 394 n (%)** | **Study 103 N = 565 n (%)** | **Study 102 N = 395 n (%)** | **Study 103 N = 564 n (%)** |
| Subjects with monotone missing data up to Week 24 | 25 (6.3) | 32 (5.7) | 26 (6.6) | 41 (7.3) |
| Subjects with ICE | 8 (2.0) | 14 (2.5) | 9 (2.3) | 17 (3.0) |
| Subjects with no ICE | 17 (4.3) | 18 (3.2) | 17 (4.3) | 24 (4.3) |
| Subjects who discontinued treatment after Week 24 | **2 (0.5)** | **1 (0.2)** | **0** | **0** |
| Subjects with monotone missing data through Week 52 | **1 (0.3)** | **0** | **3 (0.8)** | **1 (0.2)** |
| Subjects with non-missing data at Week 36 or Week 52 and did not discontinue treatment | 14 (3.6) | 17 (3.0) | 14 (3.5) | 23 (4.1) |

FAS: Full Analysis Set; ICE: intercurrent event; N; number of subjects with non-missing covariates in the respective model; n: size of subsample; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride

Note: Bolded numbers represent additional subjects considered to have data not missing at random. The number of subjects in the FAS is 398 for Study 102 and 573 for Study 103.

Further clarification was provided on the overview of participants with monotone missing data and no ICE that was given in Table 22. The majority of patients who were reported to have monotone missing data up to week 24 with no ICE had data available after week 24 and continued treatment.

*Primary endpoint: Absolute change from baseline in ppFEV1 through Week 24*

Given the assumptions regarding missing data (with and without a recorded intercurrent event) may not be in line with the treatment policy estimand, additional analyses were requested. The first analysis, MMRM2 is an extension of MMRM, which distinguishes between outcomes before and after the occurrence of the ICE by including a term to indicate ICE status in the model. The treatment difference at each visit was estimated via a weighted average, where weights were observed proportions based on ICE status within each treatment. Treatment effect through Week 24 was estimated by averaging Weeks 16 and 24 estimates. The 95% CI was estimated via 250 Bootstrap replicates. If the treatment effect through Week 24 was non-estimable for any of the replicates, the pre-specified MMRM was used for that replicate. ICE for prohibited medication and treatment discontinuation in the primary estimand were addressed.

The results for the MMRM2 approach are consistent with those from the primary analysis: Study 102 LS mean difference = 0.2 (95% CI: -0.7, 1.0), Study 103 LS mean difference = 0.2 (95% CI: -0.5, 0.9).

Key secondary endpoint: Absolute change from baseline in SwCl through Week 24

The MMRM2 analysis was also done for the secondary endpoint of SwCl. For study 102 the LS Mean difference was -8.5 (95% CI: -10.6, -6.4), and for study 103 the LS mean difference was estimated to be: -2.9 (95% CI: -4.7, -1.1). The applicant also conducted a CHMP-requested sensitivity analyses for ppFEV1 and SwCl where missing data were imputed based on treatment-naïve screening values. This imputation was conducted for

subjects in the VNZ/TEZ/D-IVA group who met one of the following criteria: 1) had an ICE unrelated to pregnancy; 2) discontinued treatment after Week 24 (unrelated to pregnancy); or 3) had monotone missing data through Week 52. The results from this analysis were consistent, leading to the same conclusions of non-inferiority and superiority for ppFEV1 and SwCl respectively. Tipping point analyses were also conducted, where it was assumed that the patients with missing data had an increasing range of worse values compared with a missing at random assumption. These analyses support a conclusion that the results are sufficiently robust.

*Key secondary endpoints: Proportion of subjects with SwCl <60 mmol/L or <30 mmol/L through Week 24 (pooled between Studies 102 and 103)*

An additional analysis was performed for which the risk ratio was estimated. For the proportion of subjects with SwCl <60 mmol/L through Week 24 the risk ratio was estimated to be 1.07 (95% CI: 1.03, 1.10) and for the proportion of subjects with SwCl <30 mmol/L through Week 24 the risk ratio was estimated to be 2.67 (95% CI: 1.91, 3.74). Separate analyses for Studies 102 and 103 were also requested. See Table 23 for these results.

**Table 23. GEE model analysis of the proportion of subjects with SwCl either <60 or <30 mmol/L through week 24**

| Analysis Set | Criteria | Observed Proportion (%) | | Estimated Relative Risk | 95% Confidence Intervals in % | | *P* value |
|---|---|---|---|---|---|---|---|
| | | ELX/TEZ/IVA | VNZ/TEZ/D-IVA | | Lower | Upper | |
| PFAS | N for ELX/TEZ/IVA=491 and N for VNZ/TEZ/D-IVA=480 | | | | | | |
| | SwCl <60 | 76.6 | 85.8 | 1.07 | 1.03 | 1.10 | <0.0001 |
| | SwCl <30 | 22.5 | 30.5 | 2.67 | 1.91 | 3.74 | <0.0001 |
| FAS (102) | N for ELX/TEZ/IVA=202 and N for VNZ/TEZ/D-IVA=196 | | | | | | |
| | SwCl <60 | 59.2 | 80.5 | 1.302 | 1.168 | 1.452 | <0.0001 |
| | SwCl <30 | 6.6 | 19.5 | 6.944 | 3.364 | 14.332 | <0.0001 |
| FAS (103) | N for ELX/TEZ/IVA=289 and N for VNZ/TEZ/D-IVA=284 | | | | | | |
| | SwCl <60 | 88.7 | 89.5 | 1.005 | 0.981 | 1.029 | 0.7003 |
| | SwCl <30 | 33.6 | 38.2 | 1.803 | 1.249 | 2.603 | 0.0016 |

D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; N: total sample size; PFAS: Pooled Full Analysis Set; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: Baseline was defined as the average of the 2 most recent pre-dose, non-missing values on or after the Day -14 visit, including unscheduled visits. If only 1 non-missing value was available during this interval, the available value was considered as baseline. A similar GEE model as the key secondary analysis was applied to each of the 20 multiply imputed datasets, and 1000 bootstrap runs were used to estimate the relative risk and 95% CI. Relative risk was based on ratio of estimated proportion from the GEE model.

### *2.5.5.3. Summary of main efficacy results*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 24. Summary of efficacy for Study 102**

| | | | |
|---|---|---|---|
| **Title:** A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VNZ Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for F508del and a Minimal Function Mutation (F/MF) | | | |
| Study identifier | Study code VX20-121-102<br>EudraCT number 2021-000712-31 | | |
| Design | Randomised, double-blind, active-controlled, multi-centre | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 52 weeks<br>4 weeks<br>As extension part, patients could roll over in a separate study |
| Hypothesis | Non-inferiority | | |
| Treatments groups | VNZ/TEZ/D-IVA | | 20 mg vanzacaftor qd / 100 mg tezacaftor qd / 250 mg deutivacaftor qd for 52 weeks<br>N = 196 (randomised and received intervention) |
| | ELX/TEZ/IVA | | 200 mg elexacaftor qd / 100 mg tezacaftor qd / 150 mg ivacaftor q12h for 52 weeks<br>N = 202 (randomised and received intervention) |
| Endpoints and definitions | Primary endpoint | ppFEV1 | Absolute change in ppFEV1 from baseline through Week 24 |
| | Key secondary endpoint | SwCl | Absolute change in SwCl from baseline through Week 24 |
| | Key secondary endpoint | Proportion of subjects with SwCl <60 mmol/L | Proportion of subjects with SwCl <60 mmol/L through Week 24 (data pooled with Study 103) |
| | Key secondary endpoint | Proportion of subjects with SwCl <30 mmol/L | Proportion of subjects with SwCl <30 mmol/L through Week 24 (data pooled with Study 103) |
| | Secondary endpoint | PEx | Number of pulmonary exacerbations through Week 52 |
| | Secondary endpoint | CFQ-R RD | Absolute change in CFQ-R RD score from baseline through Week 24 |
| | Secondary endpoint | ppFEV1 | Absolute change in ppFEV1 from baseline through Week 52 |
| | Secondary endpoint | SwCl | Absolute change in SwCl from baseline through Week 52 |
| | Secondary endpoint | Proportion of subjects with SwCl <60 mmol/L | Proportion of subjects with SwCl <60 mmol/L through Week 24 |
| | Secondary endpoint | Proportion of subjects with SwCl <30 mmol/L | Proportion of subjects with SwCl <30 mmol/L through Week 24 |
| Database lock | 14 December 2023 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis – non-inferiority** | | |

| | | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat<br>Full Analysis Set (FAS): all randomised subjects who carry any intended mutation and received at least 1 dose of study drug<br>24 weeks | | |
| Descriptive statistics and estimate variability | Treatment group | VNZ/TEZ/D-IVA | ELX/TEZ/IVA |
| | Number of subjects | 196 | 202 |
| | LS mean ppFEV1 (%) | 0.5 | 0.3 |
| | 95% CI of LS mean | -0.1, 1.1 | -0.3, 0.9 |
| | Number of PEx through week 52 | 67 | 90 |
| | Estimated event rate per year | 0.32 | 0.42 |
| | LS mean CFQ-R RD (points) | 0.5 | -1.7 |
| | 95% CI of LS mean | -1.5, 2.6 | -3.8, 0.3 |
| | LS mean ppFEV1 through week 52 (%) | 0.5 | 0.4 |
| | 95% CI of LS mean | -0.1, 1.1 | -0.3, 1.0 |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | Primary endpoint | Comparison groups | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference ppFEV1 (%) | 0.2 |
| | | 95% CI | -0.7, 1.1 |
| | | P-value (1-sided) | <0.0001 |
| | Secondary endpoint | Comparison groups | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | PEx rate difference | -0.10 |
| | | 95% CI | -0.24, 0.04 |
| | | P-value | |
| | Secondary endpoint | Comparison groups | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference CFQ-R RD (points) | 2.3 |
| | | 95% CI | -0.6, 5.2 |
| | | P-value | |
| | Secondary endpoint | Comparison groups | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference ppFEV1 Wk 52 (%) | 0.1 |
| | | 95% CI | -0.8, 1.0 |
| | | P-value | |
| Notes | | | |
| **Analysis description** | **Secondary analysis - superiority** | | |
| Analysis population and time point description | Intent to treat<br>Full Analysis Set (FAS): all randomised subjects who carry any intended mutation and received at least 1 dose of study drug<br>24 weeks | | |
| Descriptive statistics and estimate variability | Treatment group | VNZ/TEZ/D-IVA | ELX/TEZ/IVA |
| | Number of subjects | 196 | 202 |
| | LS mean SwCl (mmol/L) | -7.5 | 0.9 |
| | 95% CI of LS mean | -9.0, -6.0 | -0.6, 2.3 |

| | | | | |
|---|---|---|---|---|
| | LS mean SwCl through week 52 (mmol/L) | -7.5 | 0.5 | |
| | 95% CI of LS mean | -8.9, -6.2 | -0.8, 1.8 | |
| | Proportion of subjects with SwCl <60 mmol/L | 80.5 | 59.2 | |
| | Proportion of subjects with SwCl <30 mmol/L | 19.5 | 6.6 | |
| Effect estimate per comparison | Key Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference SwCl (mmol/L) | | -8.4 |
| | | 95% CI | | -10.5, -6.3 |
| | | P-value (2-sided) | | <0.0001 |
| | Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference SwCl Wk 52 (mmol/L) | | -8.0 |
| | | 95% CI | | -9.9, -6.1 |
| | | P-value | | |
| | Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | Estimated odds ratio proportion <60 mmol/L | | 4.28 |
| | | 95% CI | | 2.57, 7.11 |
| | | P-value | | |
| | Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | Estimated odds ratio proportion <30 mmol/L | | 7.19 |
| | | 95% CI | | 3.54, 14.59 |
| | | P-value | | |
| Notes | | | | |
| **Analysis description** | **Secondary analysis - superiority** | | | |
| Analysis population and time point description | Intent to treat<br>**Pooled Full Analysis Set (PFAS)**: all randomised subjects from Studies 102 and 103 who carry any intended mutation and received at least 1 dose of study drug 24 weeks | | | |
| Descriptive statistics and estimate variability | Treatment group | VNZ/TEZ/D-IVA | ELX/TEZ/IVA | |
| | Number of subjects | 465 | 479 | |
| | Proportion of subjects with SwCl <60 mmol/L | 85.8 | 76.6 | |
| | Proportion of subjects with SwCl <30 mmol/L | 30.5 | 22.5 | |
| Effect estimate per comparison | Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | Estimated odds ratio proportion <60 mmol/L | | 2.21 |
| | | 95% CI | | 1.55, 3.15 |
| | | P-value | | <0.0001 |
| | Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | Estimated odds ratio proportion <30 mmol/L | | 2.87 |
| | | 95% CI | | 2.00, 4.12 |
| | | P-value | | <0.0001 |
| Notes | Number of subjects is the number of subjects with non-missing SwCl at Week 16 or Week 24 | | | |

**Table 25. Summary of efficacy for Study 103**

| | | | |
|---|---|---|---|
| **Title:** A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VNZ Combination Therapy in Subjects With Cystic Fibrosis Who Are Homozygous for F508del, Heterozygous for F508del and a Gating (F/G) or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive CFTR Mutation and No F508del Mutation | | | |
| Study identifier | Study code VX20-121-103<br>EudraCT number 2021-000694-85 | | |
| Design | Randomised, double-blind, active-controlled, multi-centre | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 52 weeks<br>4 weeks<br>As extension part, patients could roll over in a separate study |
| Hypothesis | Non-inferiority | | |
| Treatments groups | VNZ/TEZ/D-IVA | | 20 mg vanzacaftor qd / 100 mg tezacaftor qd / 250 mg deutivacaftor qd for 52 weeks<br>N = 196 (randomised and received intervention) |
| | ELX/TEZ/IVA | | 200 mg elexacaftor qd / 100 mg tezacaftor qd / 150 mg ivacaftor q12h for 52 weeks<br>N = 202 (randomised and received intervention) |
| Endpoints and definitions | Primary endpoint | ppFEV1 | Absolute change in ppFEV1 from baseline through Week 24 |
| | Key secondary endpoint | SwCl | Absolute change in SwCl from baseline through Week 24 |
| | Secondary endpoint | PEx | Number of pulmonary exacerbations through Week 52 |
| | Secondary endpoint | CFQ-R RD | Absolute change in CFQ-R RD score from baseline through Week 24 |
| | Secondary endpoint | ppFEV1 | Absolute change in ppFEV1 from baseline through Week 52 |
| | Secondary endpoint | SwCl | Absolute change in SwCl from baseline through Week 52 |
| | Secondary endpoint | Proportion of subjects with SwCl <60 mmol/L | Proportion of subjects with SwCl <60 mmol/L through Week 24 |
| | Secondary endpoint | Proportion of subjects with SwCl <30 mmol/L | Proportion of subjects with SwCl <30 mmol/L through Week 24 |
| Database lock | 15 December 2023 | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis – non-inferiority** | | |
| Analysis population and time point description | Intent to treat<br>Full Analysis Set (FAS): all randomised subjects who carry any intended mutation and received at least 1 dose of study drug<br>24 weeks | | |
| Descriptive statistics and estimate variability | Treatment group | VNZ/TEZ/D-IVA | ELX/TEZ/IVA |
| | Number of subjects | 284 | 289 |
| | LS mean ppFEV1 (%) | 0.3 | 0.0 |
| | 95% CI of LS mean | -0.3, 0.7 | -0.5, 0.5 |

| | | | | |
|---|---|---|---|---|
| | Number of PEx through week 52 | | 86 | 79 |
| | Estimated event rate per year | | 0.29 | 0.26 |
| | LS mean CFQ-R RD (points) | | -1.2 | -1.2 |
| | 95% CI of LS mean | | -2.8, 0.3 | -2.7, 0.4 |
| | LS mean ppFEV1 through week 52 (%) | | 0.3 | 0.0 |
| | 95% CI of LS mean | | -0.2, 0.8 | -0.5, 0.5 |
| Effect estimate per comparison | Primary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference ppFEV1 (%) | | 0.2 |
| | | 95% CI | | -0.5, 0.9 |
| | | P-value | | <0.0001 |
| | Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | PEx rate difference | | 0.03 |
| | | 95% CI | | -0.07, 0.13 |
| | | P-value | | |
| | Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference CFQ-R RD (points) | | -0.1 |
| | | 95% CI | | -2.3, 2.1 |
| | | P-value | | |
| | Secondary endpoint | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference ppFEV1 Wk 52 (%) | | 0.3 |
| | | 95% CI | | -0.4, 1.0 |
| | | P-value | | |
| Notes | | | | |
| **Analysis description** | **Secondary analysis - superiority** | | | |
| Analysis population and time point description | Intent to treat<br>Full Analysis Set (FAS): all randomised subjects who carry any intended mutation and received at least 1 dose of study drug<br>24 weeks | | | |
| Descriptive statistics and estimate variability | Treatment group | | VNZ/TEZ/D-IVA | ELX/TEZ/IVA |
| | Number of subjects | | 284 | 289 |
| | LS mean SwCl (mmol/L) | | -5.1 | -2.3 |
| | 95% CI of LS mean | | -6.4, -3.7 | -3.6, -0.9 |
| | LS mean SwCl through week 52 (mmol/L) | | -5.0 | -2.2 |
| | 95% CI of LS mean | | -6.2, -3.7 | -3.5, -1.0 |
| | Proportion of subjects with SwCl <60 mmol/L | | 89.5 | 88.7 |
| | Proportion of subjects with SwCl <30 mmol/L | | 38.2 | 33.6 |
| Effect estimate per comparison | | Comparison groups | | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |

| | | | |
|---|---|---|---|
| | Key Secondary endpoint | LS mean difference SwCl (mmol/L) | -2.8 |
| | | 95% CI | -4.7, -0.9 |
| | | P-value (2-sided for superiority) | 0.0034 |
| | Secondary endpoint | Comparison groups | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | LS mean difference SwCl Wk 52 (mmol/L) | -2.8 |
| | | 95% CI | -4.6, -1.0 |
| | | P-value | |
| | Secondary endpoint | Comparison groups | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | Estimated odds ratio proportion <60 mmol/L | 1.1 |
| | | 95% CI | 0.65, 1.87 |
| | | P-value | |
| | Secondary endpoint | Comparison groups | VNZ/TEZ/D-IVA vs ELX/TEZ/IVA |
| | | Estimated odds ratio proportion <30 mmol/L | 2.06 |
| | | 95% CI | 1.33, 3.18 |
| | | P-value | |
| Notes | | | |

### *2.5.5.4. Clinical studies in special populations*

**Study VX21-121-105**

A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX121/Tezacaftor/Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Through 11 Years of Age

Study design

**Study 105** was an open-label, 2-part, multicohort, multicentre study in subjects heterozygous for a triple-combination-responsive mutation (TCR/any) 1 through 11 years of age. Cohorts A1 and B1 evaluated subjects 6 through 11 years of age. The main study objectives were safety and tolerability and PK. Efficacy was not an objective for Cohort A1 and a secondary objective for Cohort B1, included to support the extrapolation of efficacy from subjects ≥12 years of age. No control treatment was included, consistent with guidance on paediatric extrapolation (ICH E11).

In **Cohort A1**, subjects received VNZ 10 mg qd/TEZ 50 mg qd/D-IVA 125 mg qd. A 22-day duration was chosen (based on the half-lives of VNZ, TEZ, and D-IVA) to provide an adequate assessment of PK, safety, and tolerability of VNZ/TEZ/D-IVA before exposing subjects of the same age population to a longer duration of treatment in Cohort B1.

In **Cohort B1**, following a 4-week ELX/TEZ/IVA Run-in Period (waived for subjects on stable ELX/TEZ/IVA treatment), subjects received either VNZ 20 mg qd/TEZ 100 mg qd/ D-IVA 250 mg qd or VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 150 mg qd based on subject's body weight at Day 1. A 24-week duration of dosing was chosen to provide an adequate assessment of long-term safety based on prior CFTR modulator studies in this paediatric population.

The main inclusion criteria for Cohorts A1 and B1 were aged 6 through 11 years, TCR/any genotype, ppFEV1 ≥60%, and stable CF disease as judged by the investigator. The main exclusion criteria were generally similar to Studies 102 and 103.

Secondary efficacy endpoints defined for Cohort B1 were absolute change from baseline through Week 24 in SwCl, ppFEV1, CFQ-R RD score, BMI, weight, and their associated z-scores. These endpoints were analysed using an MMRM approach similar to that in Studies 102 and 103. Number of PEx and proportion of subjects with SwCl <60 mmol/L or <30 mmol/L were summarised descriptively.

Demographic data and baseline characteristics

A total of 78 subjects were enrolled in Cohort B1 who received at least 1 dose of VNZ/TEZ/D-IVA in the Treatment Period, 1 subject (1.3%) discontinued treatment (due to an AE) and no subjects discontinued the study.

Demographic data and baseline characteristics are provided in Table 26. Most subjects (62 [79.5%]) were on ELX/TEZ/IVA treatment prior to informed consent. Subjects with F/F, F/MF, F/G, F/RF, F/other, and TCR/any mutations defined as 1 of 178 ELX/TEZ/IVA-responsive mutations indicated for Trikafta (Kaftrio) based on *in vitro* data were eligible for the study. Most subjects had either the F/F (37 subjects [47.4%]) or F/MF genotype (24 subjects [30.8%]). Within the TCR/any category (n=11), 5 subjects had the F508del mutation on the second (any) allele, leaving 6 subjects (7.7%) of the total study population without an F508del mutation.

**Table 26. Study 105 Cohort B1: Subject demographics and baseline characteristics (FAS)**

| Characteristic | VNZ/TEZ/D-IVA N = 78 |
|---|---|
| **Subject demographics** | |
| **Age at Day 1 (years)** | |
| Mean (SD) | 9.1 (1.7) |
| Min, max | 6.2, 12.0 |
| **Sex, n (%)** | |
| Male | 44 (56.4) |
| Female | 34 (43.6) |
| **Race, n (%)** | |
| White | 71 (91.0) |
| Black or African American | 1 (1.3) |
| Not collected per local regulations | 5 (6.4) |
| More than 1 race | 1 (1.3) |
| **Geographic Region, n (%)[a]** | |
| North America | 47 (60.3) |
| Rest of World | 31 (39.7) |
| **Baseline characteristics** | |
| **Genotype group, n (%)** | |
| F/F | 37 (47.4) |
| F/MF | 24 (30.8) |
| F/G | 3 (3.8) |
| F/RF | 1 (1.3) |
| F/other | 2 (2.6) |
| TCR/any | 11 (14.1) |
| **Weight category, n (%)** | |
| <40 kg | 70 (89.7) |
| ≥40 kg | 8 (10.3) |
| **Weight (kg)** | |
| Mean (SD) | 30.21 (7.48) |
| **Weight z-score** | |
| Mean (SD) | 0.00 (0.89) |
| **BMI (kg/m2)** | |
| Mean (SD) | 16.83 (2.13) |
| **BMI z-score** | |
| Mean (SD) | 0.07 (0.87) |
| **ppFEV1 (percentage points)** | |
| Mean (SD) | 99.7 (15.1) |
| **ppFEV1 category, n (%)** | |
| <40 percentage points | 1 (1.3) |
| ≥40 to <70 percentage points | 1 (1.3) |
| ≥70 to ≤90 percentage points | 15 (19.2) |
| >90 percentage points | 60 (76.9) |
| Missing | 1 (1.3) |
| **SwCl (mmol/L)** | |
| Mean (SD) | 40.4 (20.9) |
| **SwCl category, n (%)** | |
| <30 mmol/L | 30 (38.5) |
| ≥30 to <60 mmol/L | 35 (44.9) |
| ≥60 mmol/L | 12 (15.4) |
| Missing | 1 (1.3) |
| **CFQ-R RD (points) score (child's version)** | |
| Mean (SD) | 84.8 (16.1) |

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; D-IVA: deutivacaftor; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/G: heterozygous for *F508del* and a gating mutation; F/MF: heterozygous for *F508del* and a minimal function mutation; F/RF: heterozygous for *F508del* and a residual function mutation; IVA: ivacaftor; n: size of subsample; N: total sample size; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR: triple combination responsive mutation; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: Baseline was defined as the predose Day 1 value. For subjects who were on stable ELX/TEZ/IVA, if the predose Day 1 value was missing, the most recent available predose value, including the screening assessment was used as baseline.

[a] For reporting purposes, North America included subjects from the United States, and Rest of the World included subjects from Europe and Australia.

Efficacy results

Following baseline established on ELX/TEZ/IVA in CF subjects 6-11 years, lung function was normal (Mean [SD] ppFEV1 99.7 [15.1] percentage points). Treatment with VNZ/TEZ/D-IVA maintained this benefit in ppFEV1 (LS mean absolute change from baseline through Week 24 0.0 percentage points [95% CI: -2.0, 1.9]) (Table 27).

Comparable results were found for the more sensitive lung function parameter lung clearance index (LCI), for which an LS mean absolute change from baseline through Week 24 in $LCI_{2.5}$ of -0.08 (-0.18, 0.02) was reported (Table 27).

Treatment with VNZ/TEZ/D-IVA further lowered SwCl levels (LS mean absolute change from baseline through Week 24 -8.6 [1.2] mmol/L). Nearly all subjects (94.9%; 95% CI: 87.4%, 98.6%) had SwCl below <60 mmol/L and most subjects (52.6%; 95% CI: 40.9%, 64.0%) had SwCl <30 mmol/L (Table 27). These percentages were 83.3% and 39.0% at ELX/TEZ/IVA baseline, respectively.

There were 6 PEx, of which 1 required hospitalisation or IV antibiotic therapy. Annualised event rates were 0.15 events per year and 0.03 events per year, respectively (Table 27).

Treatment with VNZ/TEZ/D-IVA resulted in improvements in CFQ-R RD score (Child's Version), with an LS mean absolute change from baseline through Week 24 of 3.9 points (95% CI: 1.5, 6.3) (Table 27).

Within-group LS mean absolute changes in growth parameters from baseline at Week 24 of VNZ/TEZ/D-IVA treatment were: BMI +0.22 kg/m2 (95% CI: 0.05, 0.38), BMI-for-age z-score -0.05 (95% CI: -0.12, 0.02), Weight +1.67 kg (95% CI: 1.34, 2.00), Weight-for-age z-score -0.02 (95% CI: -0.07, 0.03) (Table 27).

While direct comparisons cannot be made between Study 105 Cohort B1 and Studies 102 and 103 because of fundamental differences in the study design (including study duration and use of a control group), results from Study 105 Cohort B1 were generally consistent with the results from Studies 102 and 103.

**Table 27. Study 105 Cohort B1: Secondary efficacy endpoints (FAS)**

| Analysis | Statistic | VNZ/TEZ/D-IVA N = 78 |
|---|---|---|
| Absolute change from baseline in SwCl through Week 24 (mmol/L) | n<br>LS mean (SE)<br>95% CI of LS mean | 77<br>-8.6 (1.2)<br>-11.0, -6.3 |
| Proportion of subjects with SwCl <60 mmol/L through Week 24 | Baseline proportion (%)<br>Proportion (%)<br>95% CI | 84.4<br>94.9<br>87.4, 98.6 |
| Proportion of subjects with SwCl <30 mmol/L through Week 24 | Baseline proportion (%)<br>Proportion (%)<br>95% CI | 39.0<br>52.6<br>40.9, 64.0 |
| Absolute change from baseline in ppFEV1 through Week 24 (percentage points) | n<br>LS mean (SE)<br>95% CI of LS mean | 74<br>0.0 (1.0)<br>-2.0, 1.9 |
| Number of PEx through Week 24 | Number of subjects with events, n (%)<br>Number of events<br>Observed event rate per year | 6 (7.7)<br>6<br>0.15 |
| PEx requiring hospitalisation or IV antibiotic therapy | Number of subjects with events, n (%) | 1 (1.3) |

| | | |
|---|---|---|
| | Number of events<br>Observed event rate per year | 1<br>0.03 |
| Absolute change from baseline in CFQ-R RD score through Week 24 (points) | n<br>LS mean (SE)<br>95% CI of LS mean | 75<br>3.9 (1.2)<br>1.5, 6.3 |
| Absolute change from baseline in BMI at Week 24 (kg/m2) | n<br>LS mean (SE)<br>95% CI of LS mean | 78<br>0.22 (0.08)<br>0.05, 0.38 |
| Absolute change from baseline in BMI-for-age z-score at Week 24 | n<br>LS mean (SE)<br>95% CI of LS mean | 78<br>-0.05 (0.03)<br>-0.12, 0.02 |
| Absolute change from baseline in Weight at Week 24 (kg) | n<br>LS mean (SE)<br>95% CI of LS mean | 78<br>1.67 (0.17)<br>1.34, 2.00 |
| Absolute change from baseline in Weight-for-age z-score at Week 24 | n<br>LS mean (SE)<br>95% CI of LS mean | 78<br>-0.02 (0.03)<br>-0.07, 0.03 |
| Absolute change from baseline in $LCI_{2.5}$ through Week 24 | n<br>LS mean (SE)<br>95% CI of LS mean | 67<br>-0.08 (0.05)<br>(-0.18, 0.02) |

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; D-IVA: deutivacaftor; FAS: Full Analysis Set; IV: intravenous; $LCI_{2.5}$: number of lung turnovers required to reduce the tidal inert gas concentration to 1/40th of its starting value; LS: least squares; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: Analyses were based on the FAS, defined as all subjects who were enrolled and carried the intended CFTR genotype and received at least 1 dose of study drug during the Treatment Period.

#### *2.5.5.5. In vitro biomarker test for patient selection for efficacy*

Not applicable.

#### *2.5.5.6. Analysis performed across trials (pooled analyses and meta-analysis)*

Data from Studies 102 and 103 were pooled for analysis of the key secondary endpoints of proportion of subjects with SwCl either <60 mmol/L or <30 mmol/L. These pooled analyses are included in the Main studies section.

#### *2.5.5.7. Analysis of the contribution of each compound to the clinical efficacy*

A combination of mechanistic, *in vitro* and clinical data support the contribution of each component to the efficacy of VNZ/TEZ/D-IVA.

Each component of VNZ/TEZ/D-IVA has a different chemical structure. VNZ and TEZ are both correctors binding to different sites on the CFTR protein. Therefore, they may have an additive effect in facilitating the cellular processing and trafficking of select mutant forms that can cause defects throughout the CFTR protein (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone.

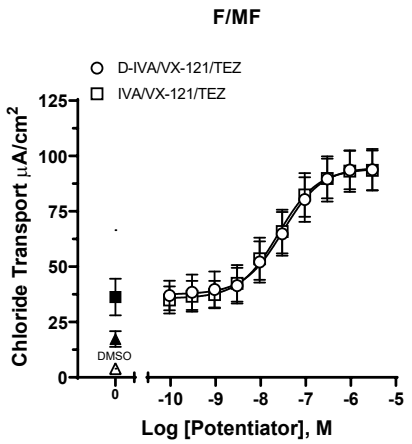
D-IVA is a deuterated isotopologue of IVA, with an identical mechanism of action as ivacaftor, i.e. potentiating the channel open probability (or gating) of the CFTR protein at the cell surface.

*In vitro* support for the contribution of each compound to the clinical efficacy

*D-IVA comparability with IVA*

A direct comparison of *in vitro* dose response in F/MF Human Bronchial Epithelial cells (HBE) demonstrated that D-IVA and IVA have equivalent effects on chloride transport (Figure 17).

**Figure 17. Concentration-response curves in F/MF-HBE cells treated with DIVA/VNZ/TEZ and IVA/VNZ/TEZ**

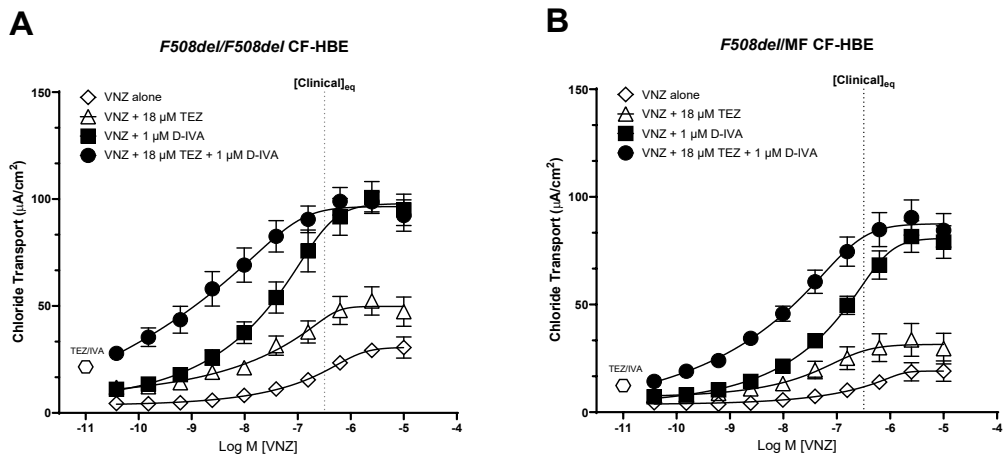



BPO: benzoyl peroxide; D-IVA: deutivacaftor; F/MF: heterozygous for F508del and a minimal function mutation; HBE: human bronchial epithelial; IVA: ivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor

*Added effect of the three compounds combined*

Figure 18 shows that the addition of D-IVA results in an increase in the function of F508del-CFTR, when added to VNZ and TEZ. Figure 18 also shows an improvement in chloride transport when TEZ is added to VNZ. These data suggest that the triple combination is more potent than the dual combinations, however the difference in efficacy at clinical equivalent concentrations was not statistically significant between the triple combination and VNZ+D-IVA in F508del/F508del-HBE cells. In F508del/MF-HBE cells there is a statistically significant difference in chloride transport at the clinically relevant concentration of VNZ in combination with TEZ and D-IVA compared to VNZ/D-IVA.

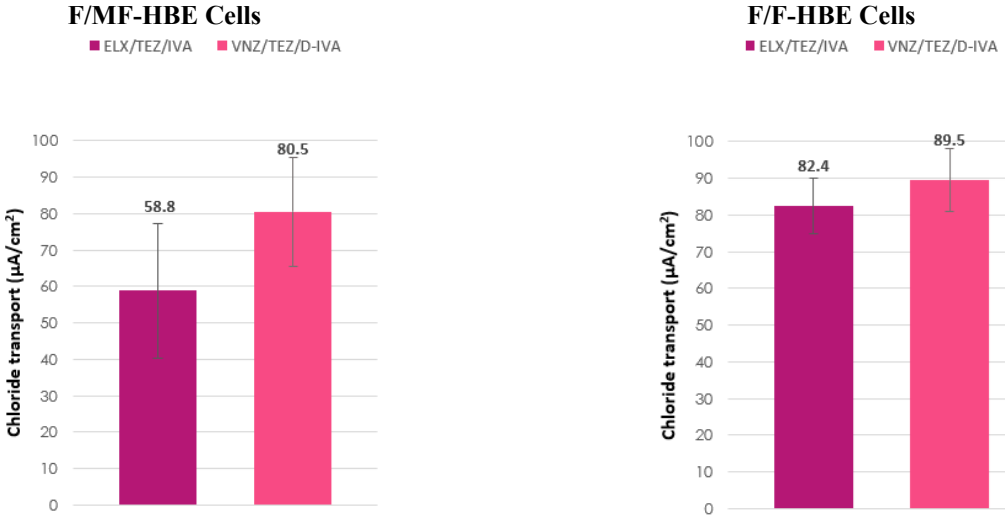
**Figure 18. Chloride transport in F/F-HBE and F/MF-HBE cells treated with VNZ alone and in combination with TEZ/D-IVA and TEZ/D-IVA**




BPO: benzoyl peroxide; CF: cystic fibrosis; DIVA: deutivacaftor; F/F: homozygous for *F508del*; HBE: human bronchial epithelial; MF: minimal function; TEZ: tezacaftor; VNZ: vanzacaftor

Additional cross study comparisons of *in vitro* HBE cell results show that VNZ/TEZ/D-IVA increased CFTR-mediated chloride transport more than ELX/TEZ/IVA in HBE cells derived from people with CF with either an F/F genotype or F/MF genotypes in which the MF mutation produces no CFTR protein (Figure 19).

**Figure 19. Cross study comparison of VNZ/TEZ/D-IVA vs ELX/TEZ/IVA in improving the Chloride Transport In vitro in HBE Cells**




D-IVA: deutivacaftor; ELX: elexacaftor; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal function mutation; HBE: human bronchial epithelial; IVA: ivacaftor; TEZ: tezacaftor; VNZ: vanzacaftor

Clinical data

The support for the clinical contribution of each compound is based on the combination of the data gathered in this package and the data obtained from the ivacaftor and TEZ/IVA and ELX/TEZ/IVA development package.

The IVA monotherapy development package showed that:

**Study 770-102 and Study 770-011**: For **F/G or G/G** subjects harbouring a specific gating mutation: IVA monotherapy has demonstrated efficacy.

**Study 770-104**: Homozygous **F/F** patients: IVA monotherapy failed to show a clinically meaning full effect on ppFEV1, while also no improvement in SwCl was demonstrated.

**D-IVA: Study 561-101** showed that D-IVA monotherapy has a similar effect compared to IVA in gating effectivity in CF patients harbouring a gating (G) mutation.

Contribution of TEZ to IVA - TEZ/IVA development:

**Study 661-106: F/F** subjects: TEZ/IVA showed a clinically relevant improvement in ppFEV1, where IVA previously failed (study 770-104)

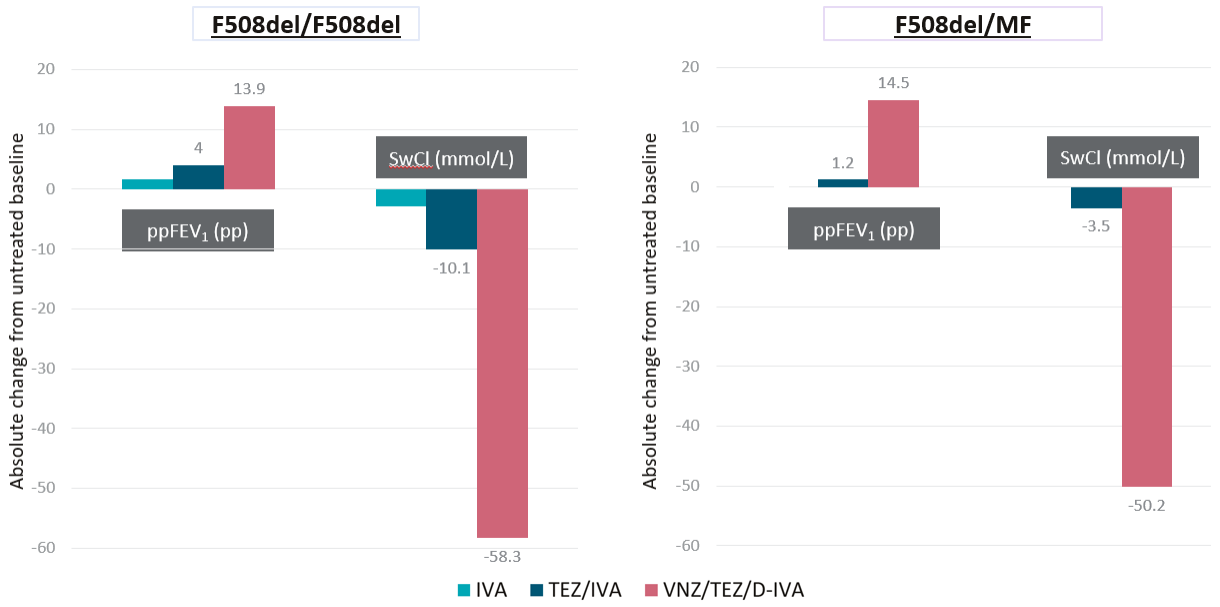
**Study 661-107: F/MF** subjects: TEZ/IVA failed to show a clinically relevant improvement in ppFEV1 while a minimal effect in SwCl was observed.

Contribution of ELX to TEZ/IVA – ELX/TEZ/IVA development:

**Study 445-103: F/F** patients: ELX/TEZ/IVA showed superiority over TEZ/IVA

**Study 445- 102: F/MF** patients: superiority demonstrated over placebo, where TEZ/IVA previously failed (study 661-107)

**Figure 20. Cross study comparison of the clinical data to show the additive benefit from the individual Components of VNZ/TEZ/D-IVA in CF subjects with an F/F or at least one F508del mutation**




CF: cystic fibrosis; D-IVA: deutivacaftor; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal function mutation; IVA: ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor; VNZ: vanzacaftor

*Notes:* ***For F/F subjects,*** *treatment with VNZ/TEZ/D-IVA resulted in improvements in $ppFEV_1$ of 0.1 percentage points compared to ELX/TEZ/IVA treatment (Study 103); treatment with ELX/TEZ/IVA in Study 445-103 resulted in improvements in $ppFEV_1$ of 10 percentage points compared to TEZ/IVA baseline, and treatment with TEZ/IVA in Study 661-106 resulted in improvements in $ppFEV_1$ of 4.0 percentage points compared to placebo. Thus, in F/F subjects, the treatment effect of VNZ/TEZ/D-IVA compared to placebo (13.9 percentage points) was estimated based on the combined results of Studies 103, 445-103, and 661-106. The estimated treatment effect for SwCl was calculated in a similar manner.*

***For F/MF subjects,*** *treatment with VNZ/TEZ/D-IVA resulted in improvements in $ppFEV_1$ of 0.2 percentage points compared to ELX/TEZ/IVA (Study 102); treatment with ELX/TEZ/IVA in Study 445-102 resulted in improvements in $ppFEV_1$ of 14.3 percentage points compared to placebo. Thus, in F/MF subjects, the treatment effect of VNZ/TEZ/D-IVA compared to placebo (14.5 percentage points) was estimated based on the combined results of Studies 102 and 445-102. The estimated treatment effect for SwCl was calculated in a similar manner.*

## 2.5.6. Discussion on clinical efficacy

This new triple fixed dose combination product (i.e. vanzacaftor, tezacaftor and deutivacaftor (VNZ/TEZ/D-IVA)) targets a broad population of patients with cystic fibrosis (CF).

The applicant applies for the following indication  recently approved by CHMP for the Kaftrio/Kalydeco triple combination).: *Alyftrek is indicated for the treatment of people with CF aged 6 years and older who have at least one non-class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2 and 5.1).*

VNZ is a new active substance. Tezacaftor is a well-known CFTR modulator. D-IVA is the isotopologue of ivacaftor and is not considered a new active substance.

The application is supported with *in vitro* and clinical data, and data obtained in the development of previous modulators, i.e. ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor.

The clinical data mainly provide support for the most common mutation, i.e. the F508del mutation present in ~80% of all pwCF in Europe. Additional clinical data are provided for 20 other mutations obtained in non-F508del patients (~3% pwCF).

No clinical data are available on the use of VNZ/TEZ/D-IVA for the remaining (rare and ultra rare) mutations.

***Design and conduct of clinical studies***

Dose finding studies

The dosing of VNZ and D-IVA was investigated in two Phase 2 studies, 101 and 561-101 respectively. Study 101 evaluated different doses of VNZ (5 mg, 10 mg, and 20 mg) in combination with TEZ 100 mg/D-IVA 150 mg once daily versus placebo in F/MF subjects, and 20 mg VNZ in combination with TEZ 100 mg/D-IVA 150 mg once daily versus TEZ/IVA in F/F subjects. Study 561-101 evaluated different doses of D-IVA (25 mg, 50 mg, 150 mg, and 250 mg) once daily versus IVA 150 mg every 12 hours in subjects with a gating (G) mutation.

Main studies

Efficacy and safety were evaluated in three Phase 3 studies in CF patients aged 6 years and older. The core efficacy studies

**Study 102** in subjects aged ⩾12 years heterozygous for F508del and a minimal function mutation (F/MF), defined as a mutation that either results in no translated CFTR protein or that is non-responsive to TEZ, IVA, or TEZ/IVA based on *in vitro* testing.

**Study 103** in subjects aged ⩾12 years a) homozygous for F508del (F/F), b) heterozygous for F508del and a gating (F/G) or residual function (F/RF) mutation, or c) with at least 1 other triple-combination-responsive mutation and no F508del mutation (TCR/non-F).

These studies were randomised, double-blind, active-controlled multicentre studies. Patients were randomised (1:1) to the VNZ/TEZ/D-IVA group or ELX/TEZ/IVA group.

Supportive paediatric study

Study 105 Cohorts A1 and B1 in subjects 6-11 years of age heterozygous for a triple-combination-responsive mutation (TCR/any) primarily evaluated safety and PK. Efficacy was a secondary objective for Cohort B1, included to support the extrapolation of efficacy from subjects ≥12 years of age. Study 105 is an open-label, single arm study. Cohorts A2, B2, A3, B3 are ongoing in younger subjects and are not considered within this procedure.

**Comparator**

The main Studies 102 and 103 were designed to demonstrate the benefit/risk upon an ELX/TEZ/IVA baseline and with ELX/TEZ/IVA as active control. Alternative placebo-controlled designs are no longer considered ethically acceptable since ELX/TEZ/IVA is available as standard of care for the included study populations.

**Duration**

Dose finding studies

The duration of both dose finding studies of 28 days is acceptable for the objective.

Main studies

For the pivotal Studies 102 and 103, a 52-week study duration was chosen mainly for safety assessment compared to the active control, while primary and key secondary efficacy analyses were assessed through week 24. Efficacy analysis through week 24 is consistent with the ELX/TEZ/IVA development programme, which was in line with the EMA guideline on CF and according to CHMP's scientific advice.

A 4-week run-in period was included to establish a stable on-treatment baseline on ELX/TEZ/IVA for all subjects at time of the study start and to homogenise the included study population. The 4-week duration is supported by results from the ELX/TEZ/IVA development programme, which showed maximal effects on ppFEV1 and SwCl were achieved by week 4. This is accepted.

For Study 105 Cohort A1, a 22-day duration was chosen based on the half-lives of VNZ, TEZ, and D-IVA for an adequate assessment of PK, safety, and tolerability before exposing subjects of the same age population to a longer duration of treatment in Cohort B1. Cohort B1 had a duration of 24 weeks and a 4-week run-in period. As efficacy was analysed in Cohort B1 only, this part of the study is discussed below.

**Inclusion and exclusion criteria**

The inclusion and exclusion criteria for the dose-response studies (101 and 561-101) and pivotal trials (102 and 103) were largely similar, except for age (dose response in adults only, pivotal also adolescents), sweat chloride (≥60 mmol/L in Study 101, unrestricted in the other studies) and the eligible CFTR genotypes. Study 101 included subjects with F/MF and F/F genotypes. Study 561-101 included subjects with an approved gating mutation in which IVA is indicated. The pivotal phase 3 trial Study 102 included F/MF subjects; while the second pivotal phase 3 trial Study 103 included F/F, F/G, F/RF, and TCR/non-F subjects. Subjects had to have FEV1 ≥40% and ≤90% (or ≤80% for subjects not on ELX/TEZ/IVA treatment in Studies 102 and 103) and stable CF. Diagnosis of CF was confirmed by the investigator.

Study 105 Cohorts A1 and B1 recruited TCR/any subjects aged 6 through 11 years with FEV1 ≥60% and stable CF disease as judged by the investigator.

The eligible TCR mutations concerned 178 mutations that have been shown to be responsive to ELX/TEZ/IVA (or components thereof) in the *in vitro* FRT assay and are included in the US (Trikafta) label.

Exclusion criteria for all studies included abnormal lab values of haemoglobin, bilirubin, or liver function enzymes, acute respiratory infection, lung infection with organisms associated with a more rapid decline in pulmonary status, renal impairment (glomerular filtration rate ≤50 mL/min/1.73 $m^2$ for subjects ≥18 years and ≤45 mL/min/1.73 $m^2$ for subjects 12-17 years) and moderate or severe hepatic impairment (Child Pugh Score B or C). These exclusion criteria are line with the previous studies of other CFTR modulator development programmes.

**Endpoints**

Dose finding

The parameters ppFEV1 and SwCl were used as endpoints in the dose-response studies 101 and 561-101. These parameters are acceptable endpoints to define the dose-response relationship.

Main studies

In both phase 3 studies 102 and 103, the trial objectives and endpoints were identical.

For the pivotal studies 102 and 103, the primary endpoint was absolute change from baseline in ppFEV1 through week 24. FEV1 is the advocated primary endpoint in the EMA guideline on CF (CHMP/EWP/9147/08). The key secondary endpoints were absolute change from baseline in SwCl through week 24 and the proportions of subjects with SwCl levels <60 mmol/L and <30 mmol/L. SwCl is a pharmacodynamic endpoint in clinical trials on CF. SwCl levels of <60 mmol/L and <30 mmol/L represent the thresholds of diagnosis of CF and normal/carrier levels, respectively.

**Non-inferiority design**

Both VX20-121-102 and VX20-121-103 studies had a non-inferiority design using a 3% non-inferiority margin.

Since the comparator ELX/TEZ/IVA is already effective in restoring lung function, the primary endpoint was tested for non-inferiority. The non-inferiority margin was set at 3 percentage points, based on a statistical approach using the Rothmann method which recommends that the non-inferiority margin preserve at least 50% of the treatment effect of the reference (ELX/TEZ/IVA) compared to placebo, where the treatment effect is estimated by the lower bound of the 95% confidence interval (CI). In the overall populations eligible for both Studies 102 and 103, the lower bound of this 95% CI is estimated to be between 7 and 12 percentage points for ppFEV1. The applicant further refers to studies on the effects of discontinuing CFTR modulator therapy that use a non-inferiority margin of ppFEV1 3 percentage points. The non-inferiority margin is, therefore, acceptable by CHMP.

Concerning assay sensitivity, the studies included subjects who were either naïve or non-naïve to CFTR modulator treatment. For the non-naïve subjects, their baseline values prior to CFTR modulator treatment were unknown. It can be assumed that the subjects who were on ELX/TEZ/IVA treatment prior to the study, once had a similar benefit of this treatment as the naïve subjects had during the run-in period of Studies 102 and 103. In addition, phase 2 study 101 showed added benefit of VNZ/TEZ/D-IVA in comparison to TEZ/IVA as well as placebo. The applicant sufficiently justified the constancy of the trial design to justify the assay sensitivity with respect to relevant genotypes. Phase 3 Studies 102 and 103 were designed to be able to detect inferiority of VNZ/TEZ/D-IVA compared to the active control (ELX/TEZ/IVA) based on historical evidence of sensitivity to drug effects, prior studies on ELX/TEZ/IVA with washout data, similarity of Studies 102 and 103 and historical CFTR modulator studies (the constancy assumption), and trial quality (minimising issues that would reduce treatment difference) consistent with ICH E10, Section 1.5.1.

**Secondary outcomes**

It is argued that lung function is not useful to discriminate any additional benefit from VNZ/TEZ/D-IVA, due to ceiling effects of both irreversible lung damage and physiological maximum lung function. The key secondary endpoint of SwCl was therefore tested for superiority. The key secondary endpoint was the absolute change from baseline in sweat chloride and the new clinical endpoints of the proportion of subjects with SwCl <60 mmol/L or <30 mmol/L at week 24 (based on the pooled analysis from Studies 102 and 103).

SwCl outcomes are regarded as supportive for the benefit risk assessment.

**Estimands**

With the exception of the populations, Studies 102 and 103 have the same estimand attributes. The primary effect of interest is the difference in the absolute change from ELX/TEZ/IVA baseline in ppFEV1 through Week

24 (averaging weeks 16 and 24) between VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups, regardless of whether patients used non-study drug CFTR modulators for more than 3 days or whether they discontinued treatment.

A supplemental estimand for the primary endpoint was defined similarly to the primary estimand, with the exception that intercurrent events were addressed using the hypothetical strategy, which targets the treatment effect that would have been obtained if patients had not used non-study drug CFTR modulators for more than 3 days and continued treatment as allocated.

For the secondary endpoints, the same two intercurrent events were identified and only the treatment policy strategy to handle these intercurrent events was pre-specified. The treatment effects intended to be measured were 1) the difference in the absolute change from ELX/TEZ/IVA baseline in SwCl through Week 24 between VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups and 2) the Odds ratio comparing the response rates in VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups.

It is supported that the applicant has defined the estimand for the non-inferiority trial, rather than defaulting to the ITT vs PP comparisons. The attribute which requires the most attention is the intercurrent events. The primary estimand as defined handles the use of non-study drug CFTR modulators for more than 3 days and discontinuation of allocated treatment using a treatment policy strategy. In the context of a non-inferiority study, it could be questioned whether this may make the treatment arms more similar. For this reason, the supplemental estimand, which targets the treatment effect that would have been obtained if patients had not used non-study drug CFTR modulators for more than 3 days and continued treatment as allocated is also important for the evaluation of non-inferiority. It is noted that the intercurrent event of use of non-study drug CFTR modulators specifies more than 3 days, this implies that use of fewer than 3 days is not of clinical relevance and would not affect the ppFEV1 values.

**Statistical analysis**

In pivotal Studies 102 and 103, the primary analysis was performed using a mixed model for repeated measures (MMRM) with change from baseline at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. The model included fixed categorical effects for treatment, visit, age at screening (<18 versus ≥18 years of age), genotype group (F/F, F/G, F/RF, TCR/non-F [Study 103 only]), and treatment-by-visit interaction, with baseline ppFEV1 and baseline SwCl as continuous covariates.

The MMRM approach is used for both the primary estimand (treatment policy) and supplemental estimand (hypothetical strategy). Missing and/or excluded data (in the case of the hypothetical) are assumed to be missing at random (MAR) conditional on observed data and covariates. It is not agreed that the MMRM approach targets the treatment policy estimand (when there are missing data) without additional information included in the model. Further analyses were requested, which better target the treatment policy estimand.

The key secondary endpoint of absolute change from baseline in SwCl through Week 24 was analysed based on an MMRM similar to the primary analysis of the primary efficacy endpoint.

The key secondary endpoints of response corresponding to SwCl <60 mmol/L or <30 mmol/L through Week 24 were analysed using a generalised estimating equations (GEE) model using the PFAS. The GEE model was used to estimate the odds ratio and included fixed categorical effects for treatment, age at screening (<18 vs ≥18 years), genotype group, visit, and treatment-by-visit interaction, with baseline ppFEV1 and baseline SwCl as continuous covariates.

Secondary efficacy endpoints in Study 105 were analysed using an MMRM approach similar to that in Studies 102 and 103.

Planned subgroup analyses were performed in Studies 102 and 103 in a manner similar to that of the primary analysis for age, baseline ppFEV1, baseline SwCl, sex and geographic region subgroups. Additionally, an ad hoc subgroup analysis was performed in Study 103 by CFTR genotype.

**Changes to the conduct of studies**

For both studies there were three global protocol amendments. The most significant changes were introduced as a part of amendment 3. During this amendment the planned sample size was increased (from 350 to 400 subjects for Study 102 and from 450 to 550 subjects for Study 103) and the duration of the treatment period was changed (from 48 weeks to 52 weeks for both studies). In general, there are no concerns in relation to amendments made to the study protocols.

***Efficacy data and additional analyses***

Dose finding

The two phase 2 studies are in principle well designed phase 2 studies but conducted in parallel. The exact similar dose of VNZ/TEZ/D-IVA combination has not been evaluated in the phase 2 studies. However, the dose selection is sufficiently supported as

- Study 561-101: D-IVA 150 mg and D-IVA 250 mg showed comparable lung function improvements, but the D-IVA 250 mg showed numerical improvements in SwCl compared with the comparator IVA 150 mg q12h.
- Study 101: VNZ variant A 10 mg (equivalent to Form D 20 mg) showed numerically larger improvements in lung function compared to the VNZ variant A 20 mg (Form D 40 mg) dose, while the improvement in SwCl were comparable in the F/MF population.
- TEZ is the same dose as applied in the ELX/TEZ/IVA and TEZ/IVA programme.

Main studies

**Demographic and baseline characteristics**

In Studies 102 and 103, demographic and baseline characteristics were generally balanced between the two treatment groups.

Overall, the mean (SD) age of subjects at Day 1 was 30.8 (11.0) years in study 102 and 33.7 (12.5) years in study 103. Less than 15% of subjects in either study was ≥12 to <18 years of age at Screening. There were 2 subjects in Study 102 and 2 subjects in Study 103 who were between 65 and 74 years of age and no subjects in either study ≥75 years of age.

Subjects were predominantly white and slightly more male subjects were enrolled in the studies. There were 172 (43.2%) subjects from Europe enrolled in Study 102 and 301 (52.5%) subjects from Europe enrolled in Study 103.

In study 102, the mean (SD) ppFEV1 at baseline was 67.1 (15.0) percentage points, 211 (53.0%) subjects had ppFEV1 <70 whereas 187 (47.0%) subjects had ppFEV1 ≥70.

In study 103, the mean (SD) ppFEV1 at baseline was 66.8 (14.7) percentage points, 327 (57.1%) subjects had ppFEV1 <70 whereas 246 (42.9%) subjects had ppFEV1 ≥70.

Only few subjects in both studies had ppFEV1 <40 or >90 at baseline.

The mean baseline SwCl value was higher in study 102 (53.9 mmol/L) than in study 103 (42.8 mmol/L). Consequently, the percentage of subjects with SwCl <30 mmol/L was lower in study 102 than in study 103.

*Genotype*

In line with the inclusion criteria, study 102 enrolled subjects who were heterozygous for F508del and an MF mutation.

In Study 103, most subjects (78%) had the F/F genotype, which is also the most prevalent genotype of the eligible genotypes in the general CF population. Only 42 subjects (7.3%) had a TCR/non-F genotype. Three subjects had a TCR allele (V754M, n=2; V562I, n=1) that is classified as non-CF-causing according to the CFTR2 database. Four other subjects had a TCR allele (D1152H, n=4) that is classified as of varying clinical consequence (VCC).

*Prior treatment*

In both studies, most subjects had received ELX/TEZ/IVA as prior medication, although the percentage of subjects treated ELX/TEZ/IVA was higher in study 102 than in study 103 (86.7% versus 67.9% respectively). Some patients (less 10% in any treatment group) in study 103 received Kalydeco, Orkambi or Symkevi.

Similar percentage of patients (~14%) in both studies had not received CFTR modulators before enrolment. Potential reasons why subjects were not on CFTR modulators prior to enrolment in Studies 102 and 103 (i.e., CFTR modulator naïve) include their geography, access to CFTR modulators, and their specific CFTR mutations. Of the 133 CFTR modulator naïve subjects enrolled in Studies 102 and 103, the majority of subjects were from countries with no commercial access (66%) to ELX/TEZ/IVA and/or had genotypes that were not eligible for commercial CFTR modulator usage (20%) during study enrolment. Demographics for CFTR modulator naïve subjects were similar to the overall study populations.

**Primary endpoint**

The primary endpoint in both studies was the absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) through Week 24.

The primary endpoint was met in both study 102 and 103.

In Study 102, from a baseline established on ELX/TEZ/IVA in the run-in period, when patients were followed up regardless of treatment discontinuation or use of another CFTR-modulator for at least 3 days (primary estimand), the difference in the absolute change from baseline in ppFEV1 through Week 24 was 0.2 percentage points (95% CI: -0.7, 1.1) between VNZ/TEZ/D-IVA and ELX/TEZ/IVA. Under the supplemental hypothetical estimand strategy (i.e. targeting the effect had patients continued allocated treatment and not used another CFTR-modulator for at least 3 days) the difference in the absolute change from baseline in ppFEV1 through Week 24 was also estimated to be 0.2 percentage points (95% CI: -0.7, 1.1).

In Study 103, when patients were followed up regardless of treatment discontinuation or use of another CFTR-modulator for at least 3 days (primary estimand), the LS mean treatment difference was 0.2 percentage points (95% CI: -0.5, 0.9). For the supplemental estimand strategy, the LS mean treatment difference was 0.3 percentage points (95% CI: -0.4, 1.0).

As the lower bound of the 95% CI in either study was greater than the pre-specified non-inferiority margin of -3.0 percentage points, these results met the primary objective of non-inferiority compared to ELX/TEZ/IVA.

There were uncertainties regarding the method of analysis to target the primary and supplemental estimands. Not all patients were able to be followed up for the full 24-week period, which has resulted in

some missing data. It is not clear how many patients experienced an intercurrent event before these data were missing. Further, it has been demonstrated that the MMRM approach, which does not make a distinction between pre- and post- intercurrent event data can lead to a bias for the treatment effects for a treatment policy strategy. Several additional analyses were therefore requested by CHMP in order to ensure robustness of the results for the primary estimand. The additional analysis, MMRM2, for which a term to indicate intercurrent event status is included in the model, were consistent with the results for the primary analysis. A "worst-case scenario" analysis, for which it was assumed that participants with missing ppFEV1 data returned to a level that was representative of the screening status of treatment-naïve participants and tipping point analyses were performed. Thus the additional analysis support a conclusion of non-inferiority.

For the supplemental hypothetical estimand strategy the MMRM assuming MAR is likely to better target this estimand as it makes the assumption that the unobserved/unused data are from the same distribution of the observed data conditional on the variables in the model.

**Key secondary endpoints**

Key secondary endpoints investigated the effect on SwCl and these secondary endpoints were met in both studies.

Treatment with VNZ/TEZ/D-IVA resulted in a larger improvement in SwCl levels compared to ELX/TEZ/IVA and the improvement was larger in the F/MF subjects in Study 102 (LS mean treatment difference -8.4 mmol/L [95% CI: -10.5, -6.3]) than in the rather heterogeneous study population of Study 103 (LS mean treatment difference -2.8 mmol/L [95% CI: -4.7, -0.9]). This is in line with the observation that subjects with more impaired baseline SwCl may show larger improvements in SwCl and clinical outcomes.-

As with the ppFEV1 outcome, the primary estimand for the secondary objective is based on a treatment policy approach, meaning that the SwCl values would be included in the analysis regardless of whether patients discontinued or used CFTR-modulator for at least 3 days. This also includes the situation where a patient initially allocated to VNZ/TEZ/D-IVA switched back to ELX/TEZ/IVA. Sensitivity analyses that examined the robustness of the results to various missing data assumptions supported the primary results.

To ensure sufficient power for the analyses of the key secondary endpoints of proportion of subjects with SwCl <60 mmol/L and <30 mmol/L, data from Studies 102 and 103 were pooled, showing higher likelihood of achieving these SwCl levels when treated with VNZ/TEZ-D-IVA compared to ELX/TEZ/IVA (odds ratios of 2.21 [95% CI: 1.55, 3.15] for <60 mmol/L and 2.87 [95% CI: 2.00, 4.12] for <30 mmol/L).

For the estimation of the percentage of "responding" patients (i.e. with SwCl <60mmol/L), patients with missing data at week 16 and week 24 were excluded from the denominator. This approach is not in line with the proposed treatment policy estimand and is likely to lead to a bias in the estimated response rate and the relative response rate.

For the estimation of the odds ratio, the applicant has used a GEE model with a logit link function and an unstructured working correlation matrix. In the presence of missing data, a GEE approach produces biased results. Further, the odds ratio is not a good measure given the high number of responders and the difficulty that prescribers and patients may have in interpreting the odds ratio. An estimate of the relative risk has been provided for the pooled population and for the separate studies Studies 102 and 103.

**Other secondary endpoints**

For all other secondary endpoints not investigating effects on SwCl (such as rates in PEx, CFQ-R RD score, ppFEV1 through Week 52 and Nutritional parameters) in both studies, the results were similar between the treatment groups.

**Subgroup analysis**

Subgroup analyses for the primary endpoint were consistent with the primary analyses, showing that irrespective of age, baseline ppFEV1, baseline SwCl, sex, geographic region, and genotype group (Study 103 only), subjects in the VNZ/TEZ/D-IVA group had similar improvements in ppFEV1 compared to subjects in the ELX/TEZ/IVA group in either study. Of note, within the 42 TCR/non-F subjects (7.3% of the study population) 22 out of 178 eligible mutations were represented in this subgroup. It is understood that due to the epidemiology, only a subset of the eligible mutations could be enrolled in the study. The 22 CFTR mutations included in the clinical development programme (of which 2 are considered non-CF-causing) are the most common non-F508del mutations, accounting for ~3% of pwCF in the proposed indication. The remaining FRT-responsive mutations included in the proposed indication also account for ~3% of pwCF, illustrating how rare these mutations are, and precluding that these mutations can be studied properly in an RCT. This is acknowledged. The applicant has therefore committed to collecting supportive post-approval efficacy data in non-F508del patients.

Subgroup analysis for the key secondary endpoint of change in SwCl from baseline were generally consistent with the result from the primary analysis, namely, that regardless of differences in age, ppFEV1 at baseline, SwCl at baseline, sex, and geographic region, subjects in the VNZ/TEZ/D-IVA group had greater reductions in SwCl compared to subjects in the ELX/TEZ/IVA group in Study 102 and Study 103, respectively. For the genotype subgroups, some subgroup analyses gave a deviating result, which could be partly due to the small numbers of included subjects in these subgroups. It should, however, also be acknowledged that this could (partly) indicate a smaller effect of VNZ/TEZ/D-IVA on SwCl levels in some genotype subgroups.

#### *2.5.6.1. Additional expert consultation*

Not applicable.

#### *Assessment of paediatric data on clinical efficacy*

A total of 57 and 79 subjects ≥12 and <18 years of age participated in Studies 102 and 103, respectively. Subgroup analysis by age (<18 versus ≥18 years) showed results in adolescents were consistent with the primary analysis for absolute change from baseline through Week 24 in ppFEV1 and SwCl.

Study 105 provided supportive efficacy data in paediatric subjects. While the study enrolled subjects with F/F, F/MF, F/G, F/RF, F/other, and TCR/any mutations, 61 out of 78 subjects (78%) had either the F/F or F/MF genotype and only 6 subjects (7.7%) had no F508del mutation. Considering the data obtained in Study 105 are supportive, this has no consequence for the outcome of the procedure.

For study 105, mean baseline SwCl levels of 40.4 (20.9) mmol/L on ELX/TEZ/IVA treatment were less than half of those seen at baseline in the ELX/TEZ/IVA pivotal Study 445-106 in F/F and F/MF subjects aged 6-11 years (102.2 mmol/L). The ELX/TEZ/IVA baseline levels in Study 105 were numerically lower than the ELX/TEZ/IVA baseline SwCl levels found in Study 102 (~54 mmol/L) and Study 103 (~43 mmol/L). After 24 weeks of VNZ/TEZ/D-IVA treatment, SwCl levels found in Study 105 were also lower than those in Studies

102 and 103, with larger proportions of subjects with SwCl levels <60 mmol/L and <30 mmol/L (Study 102: 81% and 20%; Study 103: 90% and 38%; Study 105: 95% and 53%, respectively). This is in line with literature that SwCl levels slightly increase with age.

Since efficacy was only a secondary objective, the sample size was not planned to support efficacy. Results from subgroup analyses, which have even smaller sample sizes, should be interpreted accordingly with caution. Nevertheless, subgroup analyses showed consistent results with the results reported for the general population. Regardless of differences in genotype or prior use of ELX/TEZ/IVA, levels of ppFEV1 were maintained following 24 weeks of VNZ/TEZ/D IVA treatment relative to baseline established on ELX/TEZ/IVA and reductions in SwCl relative to baseline were observed.

Other efficacy results including lung function are generally consistent with those of Studies 102 and 103, generally posing no efficacy issues regarding extrapolation of results in subjects ≥12 years towards children aged 6-11 years.

#### *2.5.6.2. Mutations without any clinical data*

**Mutations with *in vitro* FRT data only**

The representativeness of the 22 CFTR mutations of which 2 are considered non-CF-causing with clinical and FRT data for other FRT-responsive mutations is based on the positive predictive ability of the FRT assay, the mechanism of action of VNZ/TEZ/D-IVA, and the epidemiology of these mutations as the most prevalent mutations were most likely to be included in the study.

The predictiveness of a positive FRT response for a clinical response has sufficiently been substantiated for ELX/TEZ/IVA (EMEA/H/WS2551). The two triple combinations essentially only differ in the VNZ and ELX component, because D-IVA is the deuterated from of IVA, and both products contain tezacaftor. In silico, VNZ and ELX have comparable binding sites. Considering the 1) rational and similar mode of action of VNZ/TEZ/D-IVA and ELX/TEZ/IVA, 2) comparable efficacy and safety profiles in the F508del and non-F508del populations for both, and 3) the consistency in *in vitro* and clinical results between ELX/TEZ/IVA and VNZ/TEZ/D-IVA, it seems reasonable to assume that a positive FRT response is also predictive of a clinical response for VNZ/TEZ/D-IVA.

Of 475 mutations tested with VNZ/TEZ/D-IVA, 54 were not responsive to any CFTR modulator, 47 were responsive to VNZ/TEZ/D-IVA only, and the remaining 374 mutations were responsive to both VNZ/TEZ/D-IVA and ELX/TEZ/IVA. The data show that none of the tested mutations were responsive to ELX/TEZ/IVA only. This does not exclude the possibility of mutations that are responsive to ELX/TEZ/IVA but not to VNZ/TEZ/D-IVA. However, any such mutation would be very rare and only concern a very small number of patients, considering that only ultra-rare mutations have not yet been tested in the FRT assay.

**N1303K mutation**

Inclusion of the N1303K mutation is supported by the results of human bronchial epithelial (HBE) cell assays and real word clinical data generated with ELX/TEZ/IVA. Although the HBE system has not obtained regulatory qualification, it is used in research and development and clinical settings to assess responsiveness to therapy. Studies in N1303K/N1303K-HBE cells provide supportive data for efficacy of VNZ/TEZ/D-IVA for the N1303K mutation. In consideration of the justification of sufficient similarity between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, inclusion of N1303K in the indication for VNZ/TEZ/D-IVA is supported, provided that the applicant pays specific attention to patients with the N1303K mutation in the post-authorisation study.

**Non-canonical splice mutations**

For the non-canonical splice mutations, the applicant refers to the evidence of clinical responsiveness to IVA and TEZ/IVA for 5 non-canonical splice mutations, while clinical effect of ELX/TEZ/IVA was confirmed for 3 of these mutations. Based on a similar mechanism of action between ELX/TEZ/IVA and VNZ/TEZ/D-IVA, these mutations are also expected to respond to VNZ/TEZ/D-IVA, and the benefit-risk for other responsive mutations adequately informs the benefit-risk for these non-canonical splice mutations. In consideration of the justification of sufficient similarity between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, inclusion of the non-canonical splice mutations in the indication for VNZ/TEZ/D-IVA is supported, provided that the applicant pays specific attention to patients with non-canonical splice mutations in the post-authorisation study.

The applicant has committed to provide additional supportive clinical efficacy data ($ppFEV_1$) through the proposed PAES (VX24-121-107) for all people with CF who have 2 non-*F508del* mutations. This study will evaluate outcomes in the 5-year periods before and after treatment initiation with VNZ/TEZ/D-IVA, with 5 annual analysis reports planned to be submitted from 2026 through 2030. In addition to safety endpoints, this study will evaluate disease progression endpoints, including ppFEV1, BMI, and SwCl (if sufficient data are available).

The design of this PAES aligns with the PAES approved for ELX/TEZ/IVA and is acceptable. However, the proposed study VX24-121-107 should be an **Annex II condition**. In addition, the following points should be addressed:

- The applicant should pay special attention to patients with N1303K mutation and patients with non-canonical splice mutations. All efforts should be made to recruit these patients to the study and collect their efficacy data. Targets for recruitment of this group of patients should be prespecified in the study protocol.
- The group of patients with significant disease progression (as defined by the applicant) should be analysed and their underlying mutation discussed.
- Once more data on the use of VNZ/TEZ/D-IVA are generated, it will become possible to analyse the discriminatory statistics of the FRT assay for VNZ/TEZ/D-IVA with better precision. The applicant has been present this analysis together with each annual report submitted for the post-authorisation study to get confirmation that reliance on the FRT assay is also appropriate for VNZ/TEZ/D-IVA. The applicant provided a letter of commitment accordingly.

### *2.5.6.3. Supplementary studies*

**Analysis of the contribution of each compound to the clinical efficacy**

The contributive effect of ELX to TEZ/IVA has been established in the Kaftrio programme.

Supportive non-clinical data suggest that the triple combination is more potent than the dual combinations, however the difference in efficacy at clinical equivalent concentrations was not statistically significant between the triple combination and VNZ+D-IVA. In F508del/MF-HBE cells there was a statistically significant difference in chloride transport at the clinically relevant concentration of VNZ in combination with TEZ and D-IVA compared to VNZ/D-IVA.

Although the clinical implication of this difference is not fully convincing, considering that TEZ has already been approved in the triple combination ELX/TEZ/IVA and that TEZ has a different binding site than VNZ and ELX, whereas VNZ and ELX have largely overlapping binding sites, use of the triple combination is acceptable.

## 2.5.7. Conclusions on clinical efficacy

Treatment with VNZ/TEZ/D-IVA met the primary objective of non-inferiority compared to ELX/TEZ/IVA in maintaining lung function (ppFEV1) over the course of 24 weeks treatment in subjects with at least one F508del mutation or one of 22 included TCR (non-F) CFTR mutations.

Statistically significant improvements (i.e., reductions) were obtained in SwCl levels with VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA in F/MF subjects and to a lesser extent in the heterogeneous population of F/F, F/G, F/RF, and TCR/non-F subjects.

Supportive data in children with mostly F/F or F/MF genotypes showed that lung function was maintained over the course of 24 weeks on VNZ/TEZ/D-IVA treatment compared to an ELX/TEZ/IVA baseline, while improvements were found in SwCl levels. The results generally pose no efficacy issues regarding extrapolation of results in subjects ≥12 years towards children aged 6-11 years.

Considering that there is sufficient comparability between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, and the applicant committed to provide post-approval efficacy data in people with CF who have 2 non-F508del mutations, extrapolation from ELX/TEZ/IVA to VNZ/TEZ/D-IVA is acceptable. This extrapolation implies that the same broad indication can be applied to Alyftrek as has been approved for Kaftrio, i.e. "the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least 1 non-class I mutation in the CFTR gene".

However, since the level of uncertainties in respect to the potential treatment response for the non-F508del population is greater with VNZ/TEZ/D-IVA than with ELX/TEZ/IVA, the post-authorisation study for VNZ/TEZ/D-IVA should be subject to Annex II condition.

## 2.5.8. Clinical safety

Clinical safety data are derived from 17 clinical studies that evaluated VNZ and D-IVA as a monotherapy or as the VNZ/TEZ/D-IVA triple combination (TC) regimen. The VNZ/TEZ/D-IVA safety profile is primarily based on the **Pooled Safety Set**, i.e. pooled 52-week safety data for Studies 102 and 103 in CF subjects ⩾12 years of age (Table 28).

- Study 102 is a Phase 3, randomised, double-blind, controlled study evaluating the efficacy and safety of VNZ/TEZ/D-IVA in CF patients who are heterozygous for the F508del mutation and a minimal function mutation (F/MF).
- Study 103 is a Phase 3, randomised, double-blind, controlled study evaluating the efficacy and safety of VNZ/TEZ/D-IVA in CF patients homozygous for the F508del Mutation (F/F), heterozygous for F508del and a gating (F/G) or residual function (F/RF) mutation, or have at least 1 other triple combination responsive CFTR mutation and no F508del mutation.

Main supportive data is derived from **Study 105 Cohorts B1** and **open-label extension studies 104 and 106**.

- Study 105 is a Phase 3, 24 week open-label, single arm study of VNZ/TEZ/D-IVA in CF subjects 6 through 11 years of age with at least 1 triple combination responsive (TCR) mutation in the *CFTR* gene.

- Interim analyses of OLE Study 104 (for eligible subjects who completed Study 102 or Study 103) and OLE Study 106 (for eligible subjects who completed Study 105 Cohort B1) provide long-term safety data.

**Table 28. Main safety data sets**

| Purpose | Studies Included (Study Type) | Treatment Group(s) | Number of Subjects |
|---|---|---|---|
| **Core Safety Analyses** | | | |
| **Pooled Safety Set** | | | |
| To evaluate the safety profile of VNZ/TEZ/D-IVA in all CF subjects ≥12 years of age who received at least 1 dose of study drug in the Treatment Period | Study 102 (efficacy and safety) | VNZ/TEZ/D-IVA | 196 |
| | | ELX/TEZ/IVA | 202 |
| | Study 103 (efficacy and safety) | VNZ/TEZ/D-IVA | 284 |
| | | ELX/TEZ/IVA | 289 |
| **Study 105 Safety Sets** | | | |
| To evaluate the safety profile of VNZ/TEZ/D-IVA in all CF subjects 6 through 11 years of age who received at least 1 dose of study drug in the Treatment Period | Study 105 Cohort A1 (safety, tolerability, and PK) | VNZ/TEZ/D-IVA | 17 |
| | Study 105 Cohort B1 (safety, tolerability, PK, and efficacy) | VNZ/TEZ/D-IVA | 78 |

### *2.5.8.1. Patient exposure*

In total, 894 people received at least 1 dose of VNZ as either monotherapy or part of a triple combination (TC; either VNZ/TEZ/IVA or VNZ/TEZ/D-IVA) regimen, including 152 subjects who received >52 weeks and 485 subjects who received >24 weeks of VNZ/TEZ/D-IVA.

*Pooled Safety Set* - In the pooled Safety Set, 480 patients received at least 1 dose of VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd, with a mean exposure of 49.5 weeks, representing approximately 495.5 patient-years (Table 29). In the pooled safety population, 293 patients received ≥52 weeks of VNZ/TEZ/D-IVA.

Subject demographics and baseline characteristics were similar between treatment groups in both Studies 102 and 103. The majority of subjects (86.3%) were using a CFTR modulator on or prior to informed consent. In addition, 75.6% of all subjects in the pooled Safety Set received ELX/TEZ/IVA prior to study enrolment, with a median exposure of ~2 years; 13.7% of all subjects did not have a record of prior CFTR modulator use. All subjects who entered the Treatment Period received and tolerated ELX/TEZ/IVA for 4 weeks during the Run-in Period.

**Table 29. Summary of exposure (pooled safety set)**

| | ELX/TEZ/IVA N = 491 | VNZ/TEZ/D-IVA N = 480 |
|---|---|---|
| **Total exposure (patient-weeks)** | 24524.6 | 23782.9 |
| **Total exposure (patient-years)** | 510.9 | 495.5 |
| **Exposure duration (weeks)** | | |
| N | 491 | 480 |
| Mean (SD) | 49.9 (8.6) | 49.5 (9.2) |
| Median | 52.0 | 52.0 |
| Min, max | 0.1, 53.7 | 0.4, 54.1 |
| **Exposure duration by interval, n (%)** | | |
| ≤1 week | 2 (0.4) | 1 (0.2) |
| >1 to ≤2 weeks | 2 (0.4) | 1 (0.2) |
| >2 to ≤4 weeks | 2 (0.4) | 3 (0.6) |
| >4 to ≤12 weeks | 5 (1.0) | 5 (1.0) |
| >12 to ≤24 weeks | 7 (1.4) | 14 (2.9) |
| >24 to ≤36 weeks | 7 (1.4) | 7 (1.5) |
| >36 to ≤52 weeks | 315 (64.2) | 297 (61.9) |
| >52 weeks | 151 (30.8) | 152 (31.7) |

Source: ISS/Table 14.1.6
D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor; VNZ: vanzacaftor
Notes: Total exposure was defined as the sum total of the study drug exposure across all subjects. Duration of study drug exposure (weeks) = (last dose date of study drug during the Treatment Period - first dose date of study drug during the Treatment Period + 1)/7, regardless of study drug interruption. Duration of study drug exposure (years) = Duration of study drug exposure (weeks)/48; 1 year = 48 weeks.

*Study 105 Cohort B1* - In Study 105 Cohort B1, 78 subjects aged 6 through 11 years received at least 1 dose of VNZ/TEZ/D-IVA in the Treatment Period, with a mean exposure of 23.8 weeks, representing 38.7 patient years of exposure. A total of 29 patients received >24 weeks of treatment in this Cohort. Seventy (89.7%) subjects were <40 kg on Day 1 and received VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 150 mg qd. Eight (10.3%) subjects were ⩾40 kg on Day 1 and received VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd.

### *2.5.8.2. Adverse events*

Treatment Period

*Pooled Safety Set* - An overview of AEs for the Pooled Safety Set during the Treatment Period is presented in Table 30. To contextualise the data obtained in patients pre-treated with ELX/TEZ/IVA, AEs were indirectly compared to 52-week ELX/TEZ/IVA data from Studies 445-102 and 445-105 in ELX/TEZ/IVA naïve patients.

**Table 30. Summary of AEs in Studies 102 and 103 (treatment period, pooled safety set)**

| | Studies 102 and 103 | | Studies 445-102 and 445-105 (52 week data) |
|---|---|---|---|
| | ELX/TEZ/IVA N = 491 n (%) | VNZ/TEZ/D-IVA N = 480 n (%) | ELX/TEZ/IVA N = 403 n (%) |
| Number of AEs (total) | 3795 | 3551 | 3897 |
| Subjects with any AEs | 469 (95.5) | 459 (95.6) | 399 (99.0) |
| Subjects with AEs by strongest relationship | | | |
| Not related | 182 (37.1) | 151 (31.5) | 110 (27.3) |
| Unlikely related | 112 (22.8) | 140 (29.2) | 86 (21.3) |
| Possibly related | 162 (33.0) | 159 (33.1) | 182 (45.2) |
| Related | 13 (2.6) | 9 (1.9) | 21 (5.2) |
| Subjects with AEs by maximum severity | | | |
| Mild | 145 (29.5) | 166 (34.6) | 100 (24.8) |
| Moderate | 269 (54.8) | 239 (49.8) | 244 (60.5) |
| Severe | 54 (11.0) | 54 (11.3) | 53 (13.2) |
| Life-threatening | 1 (0.2) | 0 | 2 (0.5) |
| Death | 0 | 0 | 0 |
| Subjects with AEs leading to study drug discontinuation | 18 (3.7) | 18 (3.8) | 8 (2.0) |
| Subjects with AEs leading to study drug interruption | 12 (2.4) | 20 (4.2) | 43 (10.7) |
| Subjects with Grade 3 or higher AEs | 55 (11.2) | 54 (11.3) | 55 (13.6) |
| Subjects with related AEs[a] | 175 (35.6) | 168 (35.0) | 203 (50.4) |
| Subjects with SAEs | 81 (16.5) | 68 (14.2) | 82 (20.3) |
| Subjects with related SAEs[a] | 13 (2.6) | 7 (1.5) | 15 (3.7) |
| Subjects with AEs leading to death | 0 | 0 | 0 |

Source: ISS/Table 14.3.1.1.1 and Module 5.3.5.3/Studies 445-102 and 445-105/Ad hoc Table 14.3.1.1

AE: adverse event; D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: AEs were coded using MedDRA version 26.1. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category was counted only once in that category.

[a] When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing were counted.

*Study 105 Cohort B1* – An overview of AEs in Study 105 Cohort B1 Safety Set is presented in Table 31.

**Table 31. Summary of AEs in Study 105 Cohort B1 (safety set for the treatment period)**

| Category | VNZ/TEZ/D-IVA N = 78 n (%) |
|---|---|
| Subjects with any AEs | 75 (96.2) |
| Subjects with AEs by maximum severity | |
| Mild | 39 (50.0) |
| Moderate | 36 (46.2) |
| Severe | 0 |
| Life-threatening | 0 |
| Subjects with AEs by strongest relationship | |
| Not related | 29 (37.2) |
| Unlikely related | 23 (29.5) |
| Possibly related | 22 (28.2) |
| Related | 1 (1.3) |
| Subjects with AEs leading to treatment discontinuation | 1 (1.3) |
| Subjects with AEs leading to treatment interruption | 1 (1.3) |
| Subjects with related AEs | 23 (29.5) |
| Subjects with Grade 3 or higher AEs | 0 |
| Subjects with SAEs | 6 (7.7) |
| Subjects with related SAEs[a] | 1 (1.3) |
| Subjects with AEs leading to death | 0 |

Source: Study 105 CSR/Table 12-3

AE: adverse event; CSR: clinical study report; D-IVA: deutivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event; TEZ: tezacaftor; VNZ: vanzacaftor

Note: AEs were coded using MedDRA version 26.1. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.

[a] When summarizing number of subjects with related (serious) events, events with the relationship of related, possibly related, and missing were counted.

Common adverse events

*Pooled Safety Set* - AEs that occurred in ≥5% of subjects are summarised in Table 32. The incidence of AEs was generally balanced between treatment groups, except for a slightly higher incidence of AEs of influenza in the VNZ/TEZ/D-IVA group compared to the ELX/TEZ/IVA group (10.8% vs. 5.3%).

**Table 32. AEs occurring in ≥5% of subjects in any treatment group in studies 102 and 103 by PT (treatment period pooled safety set)**

| | Studies 102 and 103 | | Studies 445-102 and 445-105 (52 Weeks Data) |
|---|---|---|---|
| | ELX/TEZ/IVA N = 491 | VNZ/TEZ/D-IVA N = 480 | ELX/TEZ/IVA N = 403 |
| PT | n (%) | n (%) | n (%) |
| **Subjects with any AEs** | 469 (95.5) | 459 (95.6) | 399 (99.0%) |
| Infective PEx of CF | 158 (32.2) | 133 (27.7) | 151 (37.5) |
| Cough | 101 (20.6) | 108 (22.5) | 129 (32.0) |
| COVID-19 | 127 (25.9) | 107 (22.3) | 0 |
| Nasopharyngitis | 95 (19.3) | 102 (21.3) | 77 (19.1) |
| Headache | 63 (12.8) | 76 (15.8) | 87 (21.6) |
| Upper respiratory tract infection | 67 (13.6) | 72 (15.0) | 71 (17.6) |
| Oropharyngeal pain | 60 (12.2) | 69 (14.4) | 76 (18.9) |
| Diarrhoea | 59 (12.0) | 58 (12.1) | 55 (13.6) |
| Influenza | 26 (5.3) | 52 (10.8) | 35 (8.7) |
| Pyrexia | 50 (10.2) | 52 (10.8) | 55 (13.6) |
| Fatigue | 46 (9.4) | 51 (10.6) | 42 (10.4) |
| Nasal congestion | 47 (9.6) | 48 (10.0) | 59 (14.6) |
| Sputum increased | 50 (10.2) | 45 (9.4) | 87 (21.6) |
| Blood creatine phosphokinase increased | 41 (8.4) | 43 (9.0) | 46 (11.4) |
| ALT increased | 29 (5.9) | 38 (7.9) | 44 (10.9) |
| Rash | 22 (4.5) | 37 (7.7) | 49 (12.2) |
| Viral upper respiratory tract infection | 35 (7.1) | 37 (7.7) | 19 (4.7) |
| Rhinorrhoea | 36 (7.3) | 35 (7.3) | 46 (11.4) |
| AST increased | 27 (5.5) | 33 (6.9) | 42 (10.4) |
| Sinus congestion | 15 (3.1) | 32 (6.7) | 24 (6.0) |
| Haemoptysis | 33 (6.7) | 30 (6.3) | 36 (8.9) |
| Nausea | 30 (6.1) | 29 (6.0) | 39 (9.7) |
| Productive cough | 24 (4.9) | 28 (5.8) | 31 (7.7) |
| Abdominal pain upper | 19 (3.9) | 26 (5.4) | 20 (5.0) |
| Abdominal pain | 37 (7.5) | 25 (5.2) | 40 (9.9) |
| Back pain | 31 (6.3) | 25 (5.2) | 19 (4.7) |
| Arthralgia | 36 (7.3) | 24 (5.0) | 32 (7.9) |
| Constipation | 30 (6.1) | 22 (4.6) | 25 (6.2) |
| Sinusitis | 36 (7.3) | 19 (4.0) | 36 (8.9) |
| Dyspnoea | 28 (5.7) | 18 (3.8) | 25 (6.2) |
| Vomiting | 27 (5.5) | 15 (3.1) | 27 (6.7) |

Source: ISS/Table 14.3.1.3 and Module 5.3.5.3/Studies 445-102 and 445-105/Ad hoc Table 14.3.1.3

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: AEs were coded using MedDRA version 26.1. A subject with multiple events within a PT was counted only once in that PT. Table is sorted in descending order of frequency of the VNZ/TEZ/D-IVA column by PT. Safety Set for 445-102/105: all subjects enrolled in 445-102 who received at least 1 dose of ELX/TEZ/IVA in either 445-102 or 445-105.

*Study 105 Cohort B1* – AEs that occurred in ≥10% of subjects are summarised in Table 33.

**Table 33. AEs occurring in ≥5% of subjects by PT (study 105 cohort B1; safety set for the treatment period)**

| Preferred Term | VNZ/TEZ/D-IVA N = 78 n (%) |
|---|---|
| Subjects with any AEs | 75 (96.2) |
| Cough | 36 (46.2) |
| Pyrexia | 16 (20.5) |
| Headache | 14 (17.9) |
| Infective PEx of cystic fibrosis | 13 (16.7) |
| Oropharyngeal pain | 13 (16.7) |
| Abdominal pain | 9 (11.5) |
| Nasal congestion | 9 (11.5) |
| Rhinorrhoea | 9 (11.5) |
| Vomiting | 8 (10.3) |
| Fatigue | 7 (9.0) |
| Pharyngitis streptococcal | 7 (9.0) |
| Rhinitis | 7 (9.0) |
| Abdominal pain upper | 6 (7.7) |
| Diarrhoea | 6 (7.7) |
| Neutrophil count decreased | 6 (7.7) |
| Productive cough | 6 (7.7) |
| Upper respiratory tract infection | 6 (7.7) |
| ALT increased | 4 (5.1) |
| Ear infection | 4 (5.1) |
| Rash | 4 (5.1) |
| White blood cell count decreased | 4 (5.1) |

Source: Table 14.3.1.3b1
AE: adverse event; ALT: alanine transaminase; D-IVA: deutivacaftor; PEx: pulmonary exacerbation; TEZ: tezacaftor; VNZ: vanzacaftor
Note: AEs were coded using MedDRA version 26.1. A subject with multiple events within a PT was only counted only once in that PT. Table is sorted in descending order of frequency by Preferred Term.

Adverse events by relationship

*Pooled Safety Set* - Overall, 168 (35.0%) subjects in the VNZ/TEZ/D-IVA group and 175 (35.6%) subjects in the ELX/TEZ/IVA group had at least 1 AE considered related or possibly related to study drug. Related and possibly related AEs occurring in ⩾2% of subjects in any treatment group in the Pooled Safety Set are presented in Table 34.

**Table 34. Related and possibly related AEs occurring in ≥2% of subjects in any treatment group in Studies 102 and 103 by PT (treatment period pooled safety set)**

| Preferred Term | ELX/TEZ/IVA N = 491 n (%) | VNZ/TEZ/D-IVA N = 480 n (%) |
|---|---|---|
| Subjects with any related AEs | 175 (35.6) | 168 (35.0) |
| ALT increased | 17 (3.5) | 28 (5.8) |
| AST increased | 16 (3.3) | 25 (5.2) |
| Diarrhoea | 10 (2.0) | 23 (4.8) |
| Blood creatine phosphokinase increased | 18 (3.7) | 18 (3.8) |
| Rash | 12 (2.4) | 18 (3.8) |
| Headache | 9 (1.8) | 17 (3.5) |
| Sputum increased | 8 (1.6) | 13 (2.7) |
| Cough | 4 (0.8) | 11 (2.3) |
| Acne | 8 (1.6) | 10 (2.1) |
| Anxiety | 8 (1.6) | 10 (2.1) |
| Fatigue | 10 (2.0) | 10 (2.1) |
| Blood bilirubin increased | 11 (2.2) | 6 (1.3) |
| Infective PEx of CF | 10 (2.0) | 5 (1.0) |

Source: ISS/Table 14.3.2.3
AE: adverse event; ALT: alanine transaminase; AST: asparatate transaminase; CF: cystic fibrosis; D-IVA: deutivacaftor; ELX: elexacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor; VNZ: vanzacaftor
Notes: AEs were coded using MedDRA version 26.1. A subject with multiple events within a PT was counted only once in that category. Table is sorted in descending order of frequency by PT. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted.

*Study 105 Cohort B1* - The majority of AEs were assessed by the investigator as not related (37.2%) or unlikely related (29.5%) to study drug. There was 1 (1.3%) subject with an AE (PT: rash) assessed by the investigator as related and 22 (28.2%) subjects with AEs assessed by the investigator as possibly related. Related and possibly related AEs occurring in ⩾2% of subjects are presented in Table 35.

**Table 35. Related and Possibly Related AEs Occurring in ≥2% of Subjects by PT (Safety Set for the Treatment Period, Study 105 Cohort B1)**

| Preferred Term | VNZ/TEZ/D-IVA N = 78 n (%) |
|---|---|
| Subjects with any related AEs | 23 (29.5) |
| Headache | 5 (6.4) |
| ALT increased | 4 (5.1) |
| Neutrophil count decreased | 4 (5.1) |
| Cough | 4 (5.1) |
| Rash | 4 (5.1) |
| Fatigue | 3 (3.8) |
| White blood cell count decreased | 3 (3.8) |
| Abdominal pain | 2 (2.6) |
| Abdominal pain upper | 2 (2.6) |
| AST increased | 2 (2.6) |
| Blood creatine phosphokinase increased | 2 (2.6) |
| Decreased appetite | 2 (2.6) |
| Monocyte count decreased | 2 (2.6) |
| Oropharyngeal pain | 2 (2.6) |
| Productive cough | 2 (2.6) |
| Pyrexia | 2 (2.6) |
| Vomiting | 2 (2.6) |

Source: Table 14.3.2.3b1
AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; D-IVA: deutivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor; VNZ: vanzacaftor
Notes: AEs were coded using MedDRA version 26.1. A subject with multiple events within a PT was counted only once in that category. Table is sorted in descending order of frequency by PT. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted.

AEs by Severity

*Pooled Safety Set* - The majority of subjects with AEs had AEs that were mild or moderate in severity. In the VNZ/TEZ/D-IVA group, 54 (11.3%) subjects had at least 1 severe AE and no subjects had a life-threatening AE. In the ELX/TEZ/IVA group, 54 (11.0%) subjects had at least 1 severe AE and 1 (0.2%) subject had 1 life-threatening AE.

Severe AEs occurring in more than 2 patients were infective PEx of CF (3.8% vs. 3.5%, respectively), influenza (0.8% vs. 0.4%), ALT increased (0.8% vs. 0.2%), migraine (0.6% vs. 0%), and haemoptysis (0.6% vs. 0.2%)

*Study 105 Cohort B1* - All AEs were mild or moderate in severity. There were no AEs that were Grade 3, 4, or 5.

### *2.5.8.3. Serious adverse events, deaths, and other significant events*

SAEs

*Pooled Safety Set* - In the VNZ/TEZ/D-IVA group, 68 (14.2%) subjects had at least 1 SAE. SAEs that occurred in ≥2 subjects are presented in Table 36.

**Table 36. SAEs Occurring in ≥2 Subjects in Any Treatment Group in Studies 102 and 103 by PT (Treatment Period Pooled Safety Set)**

| | Studies 102 and 103 | | Studies 445-102 and 445-105 (52 week data) |
|---|---|---|---|
| PT | ELX/TEZ/IVA N = 491 n (%) | VNZ/TEZ/D-IVA N = 480 n (%) | ELX/TEZ/IVA N = 403 n (%) |
| Subjects with any SAEs | 81 (16.5) | 68 (14.2) | 82 (20.3) |
| Infective PEx of CF | 35 (7.1) | 29 (6.0) | 45 (11.2) |
| Influenza | 3 (0.6) | 7 (1.5) | 6 (1.5) |
| Pneumonia | 6 (1.2) | 4 (0.8) | 0 |
| Haemoptysis | 3 (0.6) | 3 (0.6) | 5 (1.2) |
| ALT increased | 2 (0.4) | 2 (0.4) | 3 (0.7) |
| AST increased | 1 (0.2) | 2 (0.4) | 3 (0.7) |
| COVID-19 | 4 (0.8) | 2 (0.4) | 0 |
| Depression | 0 | 2 (0.4) | 0 |
| Distal intestinal obstruction syndrome | 3 (0.6) | 2 (0.4) | 3 (0.7) |
| GGT increased | 1 (0.2) | 2 (0.4) | 1 (0.2) |
| Syncope | 0 | 2 (0.4) | 0 |
| Suicidal ideation | 2 (0.4) | 2 (0.4) | 0 |
| Nephrolithiasis | 2 (0.4) | 0 | 0 |
| Cholelithiasis | 3 (0.6) | 0 | 0 |
| Constipation | 3 (0.6) | 0 | 1 (0.2) |

Source: ISS/Table 14.3.2.2 and Module 5.3.5.3/Studies 445-102 and 445-105/Ad hoc Table 14.3.1.4

ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; D-IVA: deutivacaftor; ELX: elexacaftor; GGT: gamma-glutamyl transferase; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; SAE: serious adverse event; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: AEs were coded using MedDRA version 26.1. A subject with multiple events within a category (Any or PT) was counted only once in that category. Table is sorted in descending order of frequency of the VNZ/TEZ/D-IVA column by PT. Safety Set for 445-102/105: all subjects enrolled in 445-102 who received at least 1 dose of ELX/TEZ/IVA in either 445-102 or 445-105.

Related SAEs were reported for 1.5% (n=7) of patients in the VNZ/TEZ/D-IVA, and mostly consisted of transaminase elevations (Table 37).

**Table 37. Related serious treatment-emergent adverse events by system organ class and preferred term: treatment period pooled safety set**

| System Organ Class<br>Preferred Term | ELX/TEZ/IVA<br>N = 491<br>n (%) | VNZ/TEZ/D-IVA<br>N = 480<br>n (%) |
|---|---|---|
| Subjects with any related serious TEAEs | 13 (2.6) | 7 (1.5) |
| Investigations | 3 (0.6) | 3 (0.6) |
| Alanine aminotransferase increased | 2 (0.4) | 2 (0.4) |
| Aspartate aminotransferase increased | 1 (0.2) | 2 (0.4) |
| Blood bilirubin increased | 0 | 1 (0.2) |
| Blood creatine phosphokinase increased | 1 (0.2) | 1 (0.2) |
| Gamma-glutamyltransferase increased | 1 (0.2) | 1 (0.2) |
| Gastrointestinal disorders | 4 (0.8) | 1 (0.2) |
| Small intestinal obstruction | 0 | 1 (0.2) |
| Abdominal pain | 1 (0.2) | 0 |
| Distal intestinal obstruction syndrome | 1 (0.2) | 0 |
| Faecaloma | 1 (0.2) | 0 |
| Pancreatitis | 1 (0.2) | 0 |
| Hepatobiliary disorders | 0 | 1 (0.2) |
| Cholestasis | 0 | 1 (0.2) |
| Immune system disorders | 0 | 1 (0.2) |
| Hypersensitivity | 0 | 1 (0.2) |
| Metabolism and nutrition disorders | 0 | 1 (0.2) |
| Hyperphosphatasaemia | 0 | 1 (0.2) |
| Infections and infestations | 1 (0.2) | 0 |
| Meningitis aseptic | 1 (0.2) | 0 |
| Nervous system disorders | 4 (0.8) | 0 |
| Disturbance in attention | 1 (0.2) | 0 |
| Epilepsy | 1 (0.2) | 0 |
| Psychomotor hyperactivity | 1 (0.2) | 0 |
| Seizure | 1 (0.2) | 0 |
| Serotonin syndrome | 1 (0.2) | 0 |
| Psychiatric disorders | 3 (0.6) | 0 |
| Mixed anxiety and depressive disorder | 1 (0.2) | 0 |
| Suicidal ideation | 2 (0.4) | 0 |

*Study 105 Cohort B1* - Six (7.7%) subjects had at least 1 SAE. One subject had an SAE of constipation that was considered by the investigator to be possibly related to study drug. The only SAE that occurred in more than 1 subject was infective PEx of CF (2 [2.6%] subjects), 1 of which also had an SAE of failure to thrive. Other SAEs occurring in 1 (1.3%) subject each were adenovirus infection, constipation, pulmonary function test decreased, and cough.

One (1.3%) subject had an SAE of constipation that was considered possibly related to study drug.

Deaths

There were no deaths reported in the VNZ/TEZ/D-IVA clinical development programme during the TE Period. Two subjects in the Study 103 ELX/TEZ/IVA group died after the TE Period: 1 patient with septic shock, ARDS and multi-system organ failure due to pneumonia and 1 patient with adenocarcinoma pancreas. The events leading to death were not considered related or possibly related to study drug.

AEs of special interest

***Elevated Transaminase Events***

*Pooled Safety Set* – At least 1 elevated transaminase event was reported for 43 (9.0%) patients in the VNZ/TEZ/D-IVA group and 35 (7.1%) patients in the ELX/TEZ/IVA group (Table 38). The majority of events were mild or moderate in severity and resolved without treatment interruption. There were 10 subjects with elevated transaminase events that led to treatment discontinuation, 7 (1.5%) subjects in the VNZ/TEZ/D-IVA group and 3 (0.6%) subjects in the ELX/TEZ/IVA group. Two (0.4%) patients in each treatment group had a serious elevated transaminase event.

**Table 38. Studies 102 and 103 (subjects ≥12 years of age): summary of elevated transaminase events (pooled safety set)**

| | Studies 102 and 103 | | Studies 445-102 and 445-105 (52 week data) |
|---|---|---|---|
| | ELX/TEZ/IVA N = 491 n (%) | VNZ/TEZ/D-IVA N = 480 n (%) | ELX/TEZ/IVA N = 403 n (%) |
| Subjects with any events | 35 (7.1) | 43 (9.0) | 52 (12.9) |
| ALT increased | 29 (5.9) | 38 (7.9) | 44 (10.9) |
| AST increased | 27 (5.5) | 33 (6.9) | 42 (10.4) |
| Hypertransaminasaemia | 0 | 2 (0.4) | 0 |
| Subjects with any events by maximum severity | | | |
| Mild | 20 (4.1) | 24 (5.0) | 29 (7.2) |
| Moderate | 13 (2.6) | 15 (3.1) | 18 (4.5) |
| Severe | 2 (0.4) | 4 (0.8) | 5 (1.2) |
| Life-threatening | 0 | 0 | 0 |
| Subjects with events leading to treatment discontinuation | 3 (0.6) | 7 (1.5) | 4 (1.0) |
| Subjects with events leading to treatment interruption | 3 (0.6) | 5 (1.0) | 11 (2.7) |
| Subjects with related events | 22 (4.5) | 30 (6.3) | 36 (8.9%) |
| Subjects with serious events | 2 (0.4) | 2 (0.4) | 3 (0.7) |
| Subjects with related serious events[a] | 2 (0.4) | 2 (0.4) | 3 (0.7) |
| Subjects with events leading to death | 0 | 0 | 0 |

Source: ISS/Table 14.3.2.8 and Module 5.3.5.3/Studies 445-102 and 445-105/Ad hoc Table 14.3.2.1

ALT: alanine transaminase; AST: aspartate transaminase; D-IVA: deutivacaftor; ELX: elexacaftor; ISS: Integrated Summary of Safety; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: MedDRA Version 26.1 was used. A subject with multiple events within a category was counted only once in that category. PTs were sorted by alphabetical order. When summarizing number and % of subjects, a subject with multiple events within a category was counted only once in that category. Duration is only calculated for events with complete start and end dates; the time-to-onset was only calculated for events with complete start date. Safety Set for 445 102/105: all subjects enrolled in 445-102 who received at least 1 dose of Trikafta in either 445-102 or 445-105

[a] Related serious events included related, possibly related, and missing categories.

The median time-to-onset of first elevated transaminase event was 84.0 days (range: 1 to 366) in the VNZ/TEZ/D-IVA group and 108.0 days (range: 1 to 370) in the ELX/TEZ/IVA group. The incidence of elevated transaminase events was higher in the VNZ/TEZ/D-IVA group compared to the ELX/TEZ/IVA group during the first 3 months of the Treatment Period and generally balanced thereafter.

Twenty-nine (6.0%), 12 (2.5%) and 6 (1.3%) subjects in the VNZ/TEZ/D-IVA group had ALT or AST >3×, 5× and 8× ULN, respectively, compared to 15 (3.1%), 6 (1.2%) and 1 (0.2%) subjects in the ELX/TEZ/IVA group. One (0.2%) subject in the VNZ/TEZ/D-IVA group had ALT or AST >3 × ULN with concomitant increases in total bilirubin >2 × ULN. This subject had a medical history of CF liver disease with baseline ALT/AST around 3 × ULN and bilirubin levels throughout the study ranging from 0.46 to 1.87 × ULN. This subject was subsequently diagnosed with Gilbert's syndrome by genetic testing.

*Study 105 Cohort B1* - Four (5.1%) subjects had at least 1 elevated transaminase event. Four (5.1%) subjects had an AE of alanine transaminase (ALT) increased and 2 (2.6%) subjects had an AE of aspartate transaminase (AST) increased. All events were mild or moderate in severity. There were no serious elevated transaminase events or elevated transaminase events that led to treatment discontinuation or treatment interruption.

Three (3.8%), 1 (1.3%) and 0 subjects had ALT or AST >3×, 5× and 8× ULN, respectively. No subjects had elevations of ALT or AST >3 × ULN concurrent with a newly occurring elevation in total bilirubin >2 × ULN.

***Rash***

*Pooled Safety Set* - Fifty-three (11.0%) subjects in the VNZ/TEZ/D-IVA group and 38 (7.7%) subjects in the ELX/TEZ/IVA group had a least 1 rash event. The majority of events were mild or moderate in severity. One (0.2%) subject in the VNZ/TEZ/D-IVA group and no subjects in the ELX/TEZ/IVA group had a rash event that led to treatment discontinuation. Two (0.4%) subjects in the VNZ/TEZ/D-IVA group and no subjects in the ELX/TEZ/IVA group had events that led to treatment interruption. The incidence of rash was higher in the VNZ/TEZ/D-IVA group (n=26) compared to the ELX/TEZ/IVA group (n=9) during the first month of the Treatment Period and generally balanced from the 2$^{nd}$ month on (n=27 vs. n=28, respectively).

The incidence of rash events was higher in females (28 [13.0%]) than in males (25 [9.4%]) in the VNZ/TEZ/D-IVA group. In the ELX/TEZ/IVA group, 18 (7.9%) female subjects and 20 (7.6%) male subjects had rash events.

In female subjects receiving VNZ/TEZ/D-IVA, 14 (20.0%) subjects who used hormonal therapy during the study and 14 (9.7%) subjects not using hormonal therapy had rash events. In female subjects receiving ELX/TEZ/IVA, 3 (4.7%) subjects who used hormonal therapy during the study and 15 (9.1%) subjects not using hormonal therapy had rash events.

*Study 105 Cohort B1*

Four (5.1%) subjects had at least 1 rash event; all 4 subjects had an AE of rash. All events were mild in severity. There were no serious rash events; no subject had a rash event that led to treatment discontinuation or treatment interruption.

***CK Elevation***

*Pooled Safety Set* - CK elevation events occurred in 43 (9.0%) subjects in the VNZ/TEZ/D-IVA group and 41 (8.4%) subjects in the ELX/TEZ/IVA group. The AEs were mostly mild or moderate; 1 (0.2%) subject in the VNZ/TEZ/D-IVA group and 2 (0.4%) subjects in the ELX/TEZ/IVA group had a severe CK elevation event. One (0.2%) subject in the VNZ/TEZ/D-IVA group and 1 (0.2%) subject in the ELX/TEZ/IVA group had a serious CK elevation event. The 2 SAEs were the same 2 events that led to treatment discontinuation; both subjects had a history of exercise-induced CK elevations.

*Study 105 Cohort B1*

Two (2.6%) subjects had at least 1 CK elevation event; 2 subjects had an AE of blood creatine phosphokinase increased. Both events were mild in severity. There were no serious CK elevation events; no subject had a CK elevation event that led to treatment discontinuation or treatment interruption.

***Hypoglycaemia***

*Pooled Safety Set* - Eight (1.7%) subjects in the VNZ/TEZ/D-IVA group and 18 (3.7%) subjects in the ELX/TEZ/IVA group had a hypoglycaemia event. The majority of events were either mild or moderate in severity. There were no events that were serious or led to treatment interruption or discontinuation in either treatment group. Almost all patients in the VNZ/TEZ/D-IVA group with a hypoglycaemia event (7/8) had a previous history of CF related diabetes and 3/8 were on insulin. The event rate with VNZ/TEZ/D-IVA was lower (1.80 events/100 PY) than the event rate in the ELX/TEZ/IVA group (4.27/100 PY) and (indirectly compared) pooled placebo data from other studies (4.82 events/100 PY).

*Study 105 Cohort B1* - There were no hypoglycaemia events.

***Cataract***

*Pooled Safety Set* - Three (0.6%) subjects in the VNZ/TEZ/D-IVA group and 4 (0.8%) subjects in the ELX/TEZ/IVA group had an AE of cataract. All events were either mild or moderate in severity and none were visually significant. There were no events that were serious or led to treatment interruption or discontinuation in either treatment group.

*Study 105 Cohort B1* - One (1.3%) subject had a nonserious AE of cataract which was mild in severity and not visually significant. The cataract did not lead to a change in study drug dosing

***Neuropsychiatric events***

*Pooled Safety Set* - Fifty-five (11.5%) subjects in the VNZ/TEZ/D-IVA group and 59 (12.0%) subjects in the ELX/TEZ/IVA group had at least 1 neuropsychiatric event (Table 39). Serious events occurred in 4 (0.8%) subjects in the VNZ/TEZ/D-IVA group and 4 (0.8%) subjects in the ELX/TEZ/IVA group. Three (0.6%) subjects in the VNZ/TEZ/D-IVA group and 2 (0.4%) subjects in the ELX/TEZ/IVA group had events that led to treatment discontinuation. There were 22 (4.6%) subjects in the VNZ/TEZ/D-IVA arm with neuropsychiatric events that were considered at least possibly related by the investigator. These events mostly consisted of anxiety (n=11), depression/depressed mood/depressive symptoms/suicidal ideation (n=9; of which 1 event of suicidal ideation was reported) and insomnia (n=6).

**Table 39. Summary of neuropsychiatric events (pooled safety set)**

| | Studies 102 and 103 | | Studies 445-102 and 445-105 (52 week data) |
|---|---|---|---|
| | ELX/TEZ/IVA N = 491 | VNZ/TEZ/D-IVA N = 480 | ELX/TEZ/IVA N = 403 n (%) |
| Subjects with any AEs, n (%) | 59 (12.0) | 55 (11.5) | 32 (7.9) |
| Adjustment disorder with anxiety | 1 (0.2) | 0 | 0 |
| Adjustment disorder with depressed mood | 1 (0.2) | 0 | 1 (0.2) |
| Anger | 2 (0.4) | 1 (0.2) | 1 (0.2) |
| Anhedonia | 1 (0.2) | 0 | 0 |
| Anxiety | 10 (2.0) | 21 (4.4) | 9 (2.2) |
| Attention deficit hyperactivity disorder | 4 (0.8) | 1 (0.2) | 0 |
| Behaviour disorder | 1 (0.2) | 0 | 0 |
| Brain fog | 0 | 1 (0.2) | 1 (0.2) |
| Depressed mood | 7 (1.4) | 4 (0.8) | 2 (0.5) |
| Depression | 10 (2.0) | 14 (2.9) | 10 (2.5) |
| Depression suicidal | 1 (0.2) | 0 | 0 |
| Depressive symptom | 3 (0.6) | 0 | 0 |
| Disturbance in attention | 3 (0.6) | 0 | 0 |
| Generalised anxiety disorder | 1 (0.2) | 0 | 0 |
| Initial insomnia | 1 (0.2) | 3 (0.6) | 0 |
| Insomnia | 22 (4.5) | 15 (3.1) | 10 (2.5) |
| Irritability | 2 (0.4) | 1 (0.2) | 0 |
| Major depression | 0 | 1 (0.2) | 0 |
| Memory impairment | 1 (0.2) | 1 (0.2) | 0 |
| Mental fatigue | 1 (0.2) | 2 (0.4) | 0 |
| Middle insomnia | 1 (0.2) | 2 (0.4) | 0 |
| Mixed anxiety and depressive disorder | 1 (0.2) | 0 | 0 |
| Physical assault | 0 | 1 (0.2) | 0 |
| Suicidal ideation | 4 (0.8) | 2 (0.4) | 0 |
| Subjects with any events by maximum severity, n (%) | | | |
| Mild | 26 (5.3) | 28 (5.8) | 20 (5.0) |
| Moderate | 27 (5.5) | 23 (4.8) | 11 (2.7) |
| Severe | 6 (1.2) | 4 (0.8) | 0 |
| Life-threatening | 0 | 0 | 1 (0.2) |
| Subjects with events leading to treatment discontinuation, n (%) | 2 (0.4) | 3 (0.6) | 1 (0.2) |
| Subjects with events leading to treatment interruption, n (%) | 3 (0.6) | 2 (0.4) | 1 (0.2) |
| Subjects with related events, n (%) | 32 (6.5) | 22 (4.6) | 8 (2.0) |
| Subjects with serious events, n (%) | 4 (0.8) | 4 (0.8) | 1 (0.2) |
| Subjects with related serious events, n (%) | 4 (0.8) | 0 | 0 |
| Subjects with events leading to death, n (%) | 0 | 0 | 0 |
| Time-to-onset of first event (days)[a] | | | |
| Subjects with event with complete start date | 53 | 47 | 28 |
| Mean (SD) | 121.6 (105.8) | 118.2 (99.8) | 166.5 (104.2) |
| Median | 102.0 | 85.0 | 190.5 |
| Min, max | 1, 354 | 1, 323 | 1, 362 |
| Duration of events (days)[b] | | | |
| Number of events | 87 | 73 | 40 |
| Number of events with duration | 51 | 32 | 20 |
| Mean (SD) | 75.0 (78.1) | 57.8 (71.0) | 47.0 (66.3) |
| Median | 57.0 | 39.0 | 22.5 |
| Min, max | 1, 319 | 1, 285 | 1, 200 |

Source: ISS/Table 14.3.2.13 and Module 5.3.5.3/Studies 445-102 and 445-105/Ad hoc Table 14.3.2.6.
D-IVA: deutivacaftor; ELX: elexacaftor; ISS: Integrated Summary of Safety; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor; VNZ: vanzacaftor
Notes: Events were coded using MedDRA version 26.1. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related (serious) events, events with relationship of related, possibly related, and missing were counted. Safety Set for 445-102/105: all subjects enrolled in 445-102 who received at least 1 dose of Trikafta in either 445-102 or 445-105.
[a] The time-to-onset was only calculated for events with complete start date.
[b] Duration was only calculated for events with complete start and end dates.

*Study 105 Cohort B1* - Four (5.1%) subjects had at least 1 neuropsychiatric event. All events were mild in severity. There were no serious neuropsychiatric events; no subject had a neuropsychiatric event that led to treatment discontinuation or treatment interruption. Related neuropsychiatric AEs (insomnia, anxiety and aggression) were reported in 3 (3.8%) subjects.

### *2.5.8.4. Laboratory findings*

Selected serum chemistry laboratory assessments (ALT, AST, CK and blood glucose) are discussed in the AE of special interest section above.

Serum Chemistry

*Alkaline Phosphatase (ALP)*

*Pooled Safety Set* - Six (1.3%) subjects in the VNZ/TEZ/D-IVA group had ALP elevations >5 × ULN, which were generally asymptomatic, not associated with other LFT abnormalities, and resolved without intervention. These cases of isolated, asymptomatic ALP elevations did not have signs of liver or bone involvement.

*Study 105 Cohort B1* - No subjects had ALP >2.5 × ULN. There were no AEs related to ALP.

*Bilirubin*

*Pooled Safety Set* –There were small decreases in median total bilirubin levels, including indirect and direct bilirubin in the VNZ/TEZ/D-IVA group, compared to the ELX/TEZ/IVA group. There were no changes in the ELX/TEZ/IVA group. Similarly, there were decreased threshold elevations of bilirubin in the VNZ/TEZ/D-IVA group, compared to the ELX/TEZ/IVA group.

*Study 105 Cohort B1* - Results from Study 105 were generally consistent with those from Studies 102 and 103.

There were no trends observed in other chemistry parameters.

Haematology and coagulation

In the VNZ/TEZ/D-IVA group of the Pooled Safety Set and in Study 105 Cohort B1, there were small decreases from baseline in mean platelets, leukocytes, lymphocytes, and neutrophils observed. None of the AEs related to haematology or coagulation were serious or led to treatment discontinuation or interruption. In the Pooled Safety Set, AEs related to haematology and coagulation were infrequent (most PTs occurred in 1 to 2 subjects each) with a similar overall incidence across treatment groups. In Study 105 Cohort B1, AEs related to haematology that occurred in >2 subjects include neutrophil count decreased (6 [7.7%] subjects), white blood cell count decreased (4 [5.1%] subjects), and monocyte count decreased (2 [2.6%] subjects).

Other laboratory findings

There were no clinically relevant trends in urinalysis results, vital signs (including blood pressure [BP], pulse rate, temperature and respiratory rate) or pulse oximetry. There were no clinically relevant trends observed in ECG parameters in the Pooled - and Study 105 Cohort B1 Safety Sets. QTc prolongation has been evaluated in a designated trial, Study VX18-445-009, please refer to the PD section of this report.

### *2.5.8.5. In vitro biomarker test for patient selection for safety*

Not applicable.

### *2.5.8.6. Safety in special populations*

Intrinsic factors

The safety results were generally consistent in the subgroups by sex and ppFEV1. A subgroup analysis by race was not conducted because subjects were predominately White, consistent with the higher prevalence of CF in this demographic group.

*Age* - Subgroup analyses were performed by age group (subjects ≥18 years of age and subjects ≥12 to <18 years) in the Pooled Safety Set (Table 40). Related (serious) TEAEs were reported slightly more frequently in the patient group ≥18 years vs. the younger age group for the VNZ/TEZ/D-IVA arm, and TEAEs were more frequently of moderate instead of mild severity. The latter was reported for the control arm as well. However, the proportion of patients with SAEs or Grade 3+ TEAEs was more or less in line between the younger and older age group.

Safety results from Study 105 Cohorts A1 and B1 in CF subjects 6 through 11 years of age were consistent with the safety of VNZ/TEZ/D-IVA in subjects with CF ≥12 years of age.

**Table 40. Overview of treatment-emergent adverse events, by age at screening: treatment period pooled safety set**

| | ≥12 to <18 years | | | ≥18 years | | |
|---|---|---|---|---|---|---|
| | ELX/TEZ/IVA N = 69 n (%) | VNZ/TEZ/D-IVA N = 67 n (%) | Total N = 136 n (%) | ELX/TEZ/IVA N = 422 n (%) | VNZ/TEZ/D-IVA N = 413 n (%) | Total N = 835 n (%) |
| Number of TEAEs (Total) | 499 | 350 | 849 | 3296 | 3201 | 6497 |
| Subjects with any TEAEs | 63 (91.3) | 60 (89.6) | 123 (90.4) | 406 (96.2) | 399 (96.6) | 805 (96.4) |
| Subjects with TEAEs by strongest relationship | | | | | | |
| Not related | 23 (33.3) | 24 (35.8) | 47 (34.6) | 159 (37.7) | 127 (30.8) | 286 (34.3) |
| Unlikely related | 16 (23.2) | 21 (31.3) | 37 (27.2) | 96 (22.7) | 119 (28.8) | 215 (25.7) |
| Possibly related | 23 (33.3) | 15 (22.4) | 38 (27.9) | 139 (32.9) | 144 (34.9) | 283 (33.9) |
| Related | 1 (1.4) | 0 | 1 (0.7) | 12 (2.8) | 9 (2.2) | 21 (2.5) |
| Subjects with TEAEs by maximum severity | | | | | | |
| Grade 1/Mild | 25 (36.2) | 31 (46.3) | 56 (41.2) | 120 (28.4) | 135 (32.7) | 255 (30.5) |
| Grade 2/Moderate | 29 (42.0) | 20 (29.9) | 49 (36.0) | 240 (56.9) | 219 (53.0) | 459 (55.0) |
| Grade 3/Severe | 9 (13.0) | 9 (13.4) | 18 (13.2) | 45 (10.7) | 45 (10.9) | 90 (10.8) |
| Grade 4/Life-threatening | 0 | 0 | 0 | 1 (0.2) | 0 | 1 (0.1) |
| Grade 5/Death | 0 | 0 | 0 | 0 | 0 | 0 |
| Subjects with TEAEs leading to treatment discontinuation | 4 (5.8) | 1 (1.5) | 5 (3.7) | 14 (3.3) | 17 (4.1) | 31 (3.7) |
| Subjects with TEAEs leading to treatment interruption | 1 (1.4) | 2 (3.0) | 3 (2.2) | 11 (2.6) | 18 (4.4) | 29 (3.5) |
| Subjects with Grade 3+ TEAEs | 9 (13.0) | 9 (13.4) | 18 (13.2) | 46 (10.9) | 45 (10.9) | 91 (10.9) |
| Subjects with related TEAEs | 24 (34.8) | 15 (22.4) | 39 (28.7) | 151 (35.8) | 153 (37.0) | 304 (36.4) |
| Subjects with serious TEAEs | 15 (21.7) | 10 (14.9) | 25 (18.4) | 66 (15.6) | 58 (14.0) | 124 (14.9) |
| Subjects with related serious TEAEs | 4 (5.8) | 0 | 4 (2.9) | 9 (2.1) | 7 (1.7) | 16 (1.9) |
| Subjects with TEAEs leading to death | 0 | 0 | 0 | 0 | 0 | 0 |

*Hepatic impairment*

Patients with significant liver disease at screening were excluded from clinical studies. A Phase 1 nonrandomised open-label **Study 008** evaluated the PK, safety and tolerability of VX-121/TEZ/D-IVA in subjects with moderate hepatic impairment (MHI).

A total of 24 subjects were enrolled: 12 subjects with MHI (Cohort 1; Child-Pugh Class B: 7 to 9) and 12 matched healthy subjects (Cohort 2). A single oral dose of VX-121 10 mg/TEZ 50 mg/D-IVA 125 mg was administered as a fixed-dose combination (FDC) tablet.

Overall, 11 (45.8%) subjects (8 [66.7%] in Cohort 1 and 3 [25.0%] in Cohort 2) had a total of 16 AEs; all AEs were mild in severity. A total of 6 (50%) subjects had at least possibly related AEs in Cohort 1 and 2 (16.7%) subjects had at least possibly related AEs in Cohort 2. There were no Grade 3+ AEs, SAEs or deaths. AEs that occurred in ⩾2 subjects were diarrhoea (2 [16.7%] subjects) and headache (2 [16.7%] subjects). In Cohort 2, no AEs occurred in ⩾2 subjects.

*Renal impairment*

Patients with abnormal renal function at screening were excluded from clinical studies. No safety data is presented for patients with renal impairment.

Extrinsic factors

*Geographic region*

Of the 971 subjects in the Pooled Safety Set, 395 (40.7%) subjects were enrolled at sites in North America and 576 (59.3%) subjects were enrolled at sites in the rest of the world. The safety results were generally consistent in the subgroups by geographic region.

*Prior CFTR Modulator Use*

The safety profile of VNZ/TEZ/D-IVA was generally consistent across subjects who were CFTR modulator naïve and those who were previously treated with a CFTR modulator. It should be noted, however, that all subjects received a 4-week run-in on ELX/TEZ/IVA prior to randomisation to either ELX/TEZ/IVA or VNZ/TEZ/D-IVA.

An overview of AEs by prior CFTR modulator use is presented in Table 41 and AEs occurring in ⩾10% of subject in any group are presented by PT in Table 42.

**Table 41. Overview of AEs by CFTR modulator use: treatment period, pooled safety set**

| | Prior CFTRm Use = No | | Prior CFTRm Use = Yes | |
|---|---|---|---|---|
| | ELX/TEZ/IVA N = 64 n (%) | VNZ/TEZ/D-IVA N = 69 n (%) | ELX/TEZ/IVA N = 427 n (%) | VNZ/TEZ/D-IVA N = 411 n (%) |
| Number of AEs (Total) | 385 | 438 | 3410 | 3113 |
| Subjects with any AEs | 55 (85.9) | 60 (87.0) | 414 (97.0) | 399 (97.1) |
| Subjects with AEs by strongest relationship | | | | |
| Not related | 16 (25.0) | 23 (33.3) | 166 (38.9) | 128 (31.1) |
| Unlikely related | 11 (17.2) | 10 (14.5) | 101 (23.7) | 130 (31.6) |
| Possibly related | 25 (39.1) | 23 (33.3) | 137 (32.1) | 136 (33.1) |
| Related | 3 (4.7) | 4 (5.8) | 10 (2.3) | 5 (1.2) |
| Subjects with AEs by maximum severity | | | | |
| Grade 1/Mild | 15 (23.4) | 19 (27.5) | 130 (30.4) | 147 (35.8) |
| Grade 2/Moderate | 29 (45.3) | 32 (46.4) | 240 (56.2) | 207 (50.4) |
| Grade 3/Severe | 11 (17.2) | 9 (13.0) | 43 (10.1) | 45 (10.9) |
| Grade 4/Life-threatening | 0 | 0 | 1 (0.2) | 0 |
| Grade 5/Death | 0 | 0 | 0 | 0 |
| Subjects with AEs leading to treatment discontinuation | 4 (6.3) | 2 (2.9) | 14 (3.3) | 16 (3.9) |
| Subjects with AEs leading to treatment interruption | 4 (6.3) | 1 (1.4) | 8 (1.9) | 19 (4.6) |
| Subjects with Grade 3+ AEs | 11 (17.2) | 9 (13.0) | 44 (10.3) | 45 (10.9) |
| Subjects with related AEs | 28 (43.8) | 27 (39.1) | 147 (34.4) | 141 (34.3) |
| Subjects with SAEs | 10 (15.6) | 6 (8.7) | 71 (16.6) | 62 (15.1) |
| Subjects with related sSAEs | 2 (3.1) | 2 (2.9) | 11 (2.6) | 5 (1.2) |
| Subjects with AEs leading to death | 0 | 0 | 0 | 0 |

Source: ISS/Ad hoc Table 14.3.1.1.1

AE: adverse event; CFTRm: CFTR modulator; D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: AEs were coded using MedDRA version 26.1. Prior CFTR modulator use includes the most recent CFTR modulator prior to informed consent for each subject. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing are counted.

**Table 42. AEs Occurring in ≥10% in any group by PT, by CFTR modulator use: treatment period, pooled safety set**

| | Prior CFTRm Use = No | | Prior CFTRm Use = Yes | |
|---|---|---|---|---|
| | ELX/TEZ/IVA N = 64 n (%) | VNZ/TEZ/D-IVA N = 69 n (%) | ELX/TEZ/IVA N = 427 n (%) | VNZ/TEZ/D-IVA N = 411 n (%) |
| Subjects with any AEs | 55 (85.9) | 60 (87.0) | 414 (97.0) | 399 (97.1) |
| Infective PEx of CF | 15 (23.4) | 12 (17.4) | 143 (33.5) | 121 (29.4) |
| Cough | 5 (7.8) | 13 (18.8) | 96 (22.5) | 95 (23.1) |
| COVID-19 | 18 (28.1) | 18 (26.1) | 109 (25.5) | 89 (21.7) |
| Nasopharyngitis | 12 (18.8) | 15 (21.7) | 83 (19.4) | 87 (21.2) |
| Headache | 4 (6.3) | 11 (15.9) | 59 (13.8) | 65 (15.8) |
| Oropharyngeal pain | 5 (7.8) | 6 (8.7) | 55 (12.9) | 63 (15.3) |
| Upper respiratory tract infection | 13 (20.3) | 21 (30.4) | 54 (12.6) | 51 (12.4) |
| Diarrhoea | 6 (9.4) | 9 (13.0) | 53 (12.4) | 49 (11.9) |
| Fatigue | 6 (9.4) | 4 (5.8) | 40 (9.4) | 47 (11.4) |
| Influenza | 2 (3.1) | 5 (7.2) | 24 (5.6) | 47 (11.4) |
| Nasal congestion | 3 (4.7) | 4 (5.8) | 44 (10.3) | 44 (10.7) |
| Pyrexia | 5 (7.8) | 8 (11.6) | 45 (10.5) | 44 (10.7) |
| Sputum increased | 5 (7.8) | 7 (10.1) | 45 (10.5) | 38 (9.2) |
| Blood creatine phosphokinase increased | 9 (14.1) | 6 (8.7) | 32 (7.5) | 37 (9.0) |
| ALT increased | 5 (7.8) | 8 (11.6) | 24 (5.6) | 30 (7.3) |
| Viral upper respiratory tract infection | 3 (4.7) | 7 (10.1) | 32 (7.5) | 30 (7.3) |
| Rash | 4 (6.3) | 8 (11.6) | 18 (4.2) | 29 (7.1) |
| AST increased | 7 (10.9) | 8 (11.6) | 20 (4.7) | 25 (6.1) |

Source: ISS/Ad hoc Table 14.3.1.3.1

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; CFTRm: CFTR modulator; COVID-19: coronavirus disease-2019; D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: AEs were coded using MedDRA version 26.1. Prior CFTR modulator use includes the most recent CFTR modulator prior to informed consent for each subject. A subject with multiple events within a category (Any or PT) is counted only once in that category. Table is sorted in descending order of frequency of VNZ/TEZ/D-IVA in the Prior CFTRm Use = Yes column by PT.

### *2.5.8.7. Immunological events*

In the *Pooled Safety Set*, there were 3 (0.6%) immunological events reported for the VNZ/TEZ/D-IVA arm vs. 0 in the ELX/TEZ/IVA arm. These three events consisted of one SAE of maculopapular rash (see section TEAEs of special interest) and two hypersensitivity AEs (worsening environmental allergy and allergy reaction to another medicinal product). There were no cases of anaphylaxis or angioedema in either arm.

In *Study 105 Cohort B1*, there were no events of anaphylaxis, angioedema, drug hypersensitivity, or hypersensitivity.

### *2.5.8.8. Safety related to drug-drug interactions and other interactions*

Please refer to the PK section of this report.

### *2.5.8.9. Discontinuation due to adverse events*

*Pooled Safety Set* - Eighteen (3.8%) subjects in the VNZ/TEZ/D-IVA group and 18 (3.7%) subjects in the ELX/TEZ/IVA group discontinued study drug due to an AE. AEs that led to treatment discontinuation occurring in ≥2 subjects in any treatment group are presented in Table 43.

**Table 43. AEs leading to treatment discontinuation occurring in ≥2 subjects in any treatment group (pooled safety set)**

| | Studies 102 and 103 | | Studies 445-102 and 445-105 (52 week data) |
|---|---|---|---|
| | ELX/TEZ/IVA N = 491 | VNZ/TEZ/D-IVA N = 480 | ELX/TEZ/IVA N = 403 |
| PT | n (%) | n (%) | n (%) |
| Subjects with any AEs leading to treatment discontinuation | 18 (3.7) | 18 (3.8) | 8 (2.0) |
| ALT increased | 3 (0.6) | 7 (1.5) | 4 (1.0) |
| AST increased | 3 (0.6) | 6 (1.3) | 4 (1.0) |
| Fatigue | 2 (0.4) | 3 (0.6) | 0 |
| Blood alkaline phosphatase increased | 1 (0.2) | 2 (0.4) | 0 |
| Blood bilirubin increased | 0 | 2 (0.4) | 0 |
| Blood bilirubin unconjugated increased | 0 | 2 (0.4) | 0 |
| Cough | 1 (0.2) | 2 (0.4) | 0 |
| Dysphonia | 0 | 2 (0.4) | 0 |
| Anxiety | 0 | 2 (0.4) | 0 |
| Depression | 0 | 2 (0.4) | 1 (0.2) |
| Pulmonary function test decreased | 2 (0.4) | 0 | 0 |

Source: ISS/Table 14.3.2.5 and Module 5.3.5.3/Studies 445-102 and 445-105/Ad hoc Table 14.3.1.6
AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; D-IVA: deutivacaftor; ELX: elexacaftor; ISS: Integrated Summary of Safety; IVA: ivacaftor; n: size of subsample; N: total sample size TEZ: tezacaftor; VNZ: vanzacaftor
Notes: AEs were coded using MedDRA version 26.1. A subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of frequency of the VNZ/TEZ/D-IVA column. Safety Set for 445-102/105: all subjects enrolled in 445-102 who received at least 1 dose of Trikafta in either 445-102 or 445-105.

*Study 105 Cohort B1* – One (1.3%) patient had AEs of cough and fatigue that led to treatment discontinuation. The events were assessed by the investigator as mild in severity and possibly related to study drug.

**Long term safety data**

Open-label extension Study 104 (for eligible subjects who completed Study 102 or Study 103; n=822) and open-label extension Study 106 (for eligible subjects who completed Study 105 Cohort B1, n=75) are ongoing and are designed to evaluate the additional long-term safety of VNZ/TEZ/DIVA for up to an additional 96 weeks of treatment.

Overviews of AEs in Studies 104 and 106 and their respective parent studies at the interim data cutoff date of 15 May 2024 are presented in Table 44 and Table 45.

**Table 44. Exposure-adjusted overview of AEs in studies 102, 103 and 104 (treatment period and OLE pooled safety set)**

| | ELX/TEZ/IVA N = 491 | | VNZ/TEZ/D-IVA N = 480 | | 121-104 Open-label Extension Study N = 822 | |
|---|---|---|---|---|---|---|
| | n (%) | Events/100PY | n (%) | Events/100PY | n (%) | Events/100PY |
| Number of AEs (Total) | 3795 | -- | 3551 | -- | 6508 | -- |
| Total duration of TE Period in 100 PY | -- | 5.15 | -- | 5.00 | -- | 10.61 |
| Subjects with any AEs | 469 (95.5) | 736.87 | 459 (95.6) | 709.91 | 778 (94.6) | 613.50 |
| Subjects with AEs by strongest relationship | | | | | | |
| Not related | 182 (37.1) | -- | 151 (31.5) | -- | 318 (38.7) | -- |
| Unlikely related | 112 (22.8) | -- | 140 (29.2) | -- | 212 (25.8) | -- |
| Possibly related | 162 (33.0) | -- | 159 (33.1) | -- | 229 (27.9) | -- |
| Related | 13 (2.6) | -- | 9 (1.9) | -- | 19 (2.3) | -- |
| Subjects with AEs by maximum severity | | | | | | |
| Grade 1/Mild | 145 (29.5) | -- | 166 (34.6) | -- | 263 (32.0) | -- |
| Grade 2/Moderate | 269 (54.8) | -- | 239 (49.8) | -- | 444 (54.0) | -- |
| Grade 3/Severe | 54 (11.0) | -- | 54 (11.3) | -- | 69 (8.4) | -- |
| Grade 4/Life-threatening | 1 (0.2) | -- | 0 | -- | 2 (0.2) | -- |
| Grade 5/Death | 0 | -- | 0 | -- | 0 | -- |
| Subjects with AEs leading to study drug discontinuation | 18 (3.7) | 5.24 | 18 (3.8) | 9.00 | 18 (2.2) | 2.17 |
| Subjects with AEs leading to study drug interruption | 12 (2.4) | 5.05 | 20 (4.2) | 6.00 | 20 (2.4) | 4.24 |
| Subjects with Grade 3+ AEs | 55 (11.2) | 17.48 | 54 (11.3) | 20.19 | 71 (8.6) | 10.56 |
| Subjects with related AEs | 175 (35.6) | 93.01 | 168 (35.0) | 90.16 | 248 (30.2) | 57.13 |
| Subjects with serious AEs | 81 (16.5) | 22.33 | 68 (14.2) | 20.39 | 119 (14.5) | 16.21 |
| Subjects with related serious AEs | 13 (2.6) | 3.88 | 7 (1.5) | 2.20 | 4 (0.5) | 0.38 |
| Subjects with AEs leading to death | 0 | 0 | 0 | 0 | 0 | 0 |

Source: ISS/Ad Hoc Table 14.3.1.1.1

AE: adverse event; D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; OLE: open-label extension; PY: patient years; TE: Treatment-emergent; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: Events/100PY: number of events per 100 patient years (336 days = 48 weeks per year) = number of events / total duration of TE Period for the Treatment Period in 100PY. When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing are counted.

**Table 45. Exposure-adjusted overview of AEs in studies 105 (Cohort B1) and 106 (treatment period and OLE safety set)**

| | VNZ/TEZ/D-IVA N = 78 | | 121-106 Open-label Extension Study N = 75 | |
|---|---|---|---|---|
| | n (%) | Events/100PY | n (%) | Events/100PY |
| Number of AEs (Total) | 429 | -- | 500 | -- |
| Total duration of TE Period in 100 PY | -- | 0.39 | -- | 0.67 |
| Subjects with any AEs | 75 (96.2) | 1101.01 | 71 (94.7) | 745.04 |
| Subjects with AEs by strongest relationship | | | | |
| Not related | 29 (37.2) | -- | 31 (41.3) | -- |
| Unlikely related | 23 (29.5) | -- | 26 (34.7) | -- |
| Possibly related | 22 (28.2) | -- | 12 (16.0) | -- |
| Related | 1 (1.3) | -- | 2 (2.7) | -- |
| Subjects with AEs by maximum severity | | | | |
| Grade 1/Mild | 39 (50.0) | -- | 35 (46.7) | -- |
| Grade 2/Moderate | 36 (46.2) | -- | 32 (42.7) | -- |
| Grade 3/Severe | 0 | -- | 4 (5.3) | -- |
| Grade 4/Life-threatening | 0 | -- | 0 | -- |
| Grade 5/Death | 0 | -- | 0 | -- |
| Subjects with AEs leading to study drug discontinuation | 1 (1.3) | 5.13 | 2 (2.7) | 8.94 |
| Subjects with AEs leading to study drug interruption | 1 (1.3) | 2.57 | 2 (2.7) | 2.98 |
| Subjects with Grade 3+ AEs | 0 | 0 | 4 (5.3) | 5.96 |
| Subjects with related AEs | 23 (29.5) | 218.15 | 14 (18.7) | 52.15 |
| Subjects with serious AEs | 6 (7.7) | 17.97 | 9 (12.0) | 16.39 |
| Subjects with related serious AEs | 1 (1.3) | 2.57 | 1 (1.3) | 1.49 |
| Subjects with AEs leading to death | 0 | 0 | 0 | 0 |

Source: 121-105 Cohort B1/Ad Hoc Table 14.3.1.1.1

AE: adverse event; D-IVA: deutivacaftor; n: size of subsample; N: total sample size; OLE: open-label extension; PY: patient years; TE: Treatment-emergent; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: Events/100PY: number of events per 100 patient years (336 days = 48 weeks per year) = number of events / total duration of TE Period for the Treatment Period in 100PY. When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. When summarizing number of subjects with related (serious) AEs, AEs with relationship of related, possibly related, and missing are counted.

Narratives are presented for subjects who had an SAE, death, pregnancy, and/or AE leading to treatment discontinuation in Study 104 or Study 106 as of the interim cutoff date of 12 February 2024. As of this date, the majority of subjects enrolled in Study 104 had received at least 24 weeks of VNZ/TEZ/D-IVA treatment

and the majority of subjects enrolled in Study 106 had received at least 16 weeks of VNZ/TEZ/D-IVA treatment. SAEs occurring in ⩾2 subjects are summarised in Table 46 (Study 104); in Study 106, SAEs were reported for 4 (5.3%) patients. The only SAE that occurred in ⩾2 subjects was infective PEx of CF (2 [2.7%] subjects). Treatment discontinuations due to AEs was reported for 13 (1.6%) patients in Study 104. Of these events, transaminases increased and dyspnoea occurred in more than 1 patient: 0.2% each. In study 106, treatment discontinuations due to AEs were reported for 2 patients (2.7%), of which no events were reported for more than 1 patient). There were no deaths reported for the two OLE studies.

**Table 46. Study 104: SAEs occurring in ≥2 subjects by PT - OL safety period**

| PT | Any VNZ/TEZ/D-IVA N = 822 n (%) |
|---|---|
| Subjects with any SAE | 72 (8.8) |
| Infective PEx of CF | 24 (2.9) |
| Pneumonia | 6 (0.7) |
| Influenza | 2 (0.2) |
| Nephrolithiasis | 2 (0.2) |
| Haemoptysis | 2 (0.2) |

Source: data on file

AE: adverse event; CF: cystic fibrosis; COVID-19: coronavirus disease-2019; DIOS: distal intestinal obstruction syndrome; D-IVA: deutivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; SAE: serious adverse event; TEZ: tezacaftor; VNZ: vanzacaftor

Notes: AEs were coded using MedDRA version 26.1. A subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of frequency of the Any VNZ/TEZ/D-IVA column by PT.

#### *2.5.8.10. Post marketing experience*

Not applicable.

## 2.5.9. Discussion on clinical safety

The safety profile is primarily based on the Pooled Safety Set of Study 102 and 103 in CF patients 12 years and older. Main supportive data is derived from Study 105 Cohort B1 in CF patients 6 through 11 years of age. It is acknowledged that safety data from Study 105 were evaluated separately from Studies 102 and 103 due to differences in study design. Please refer to the clinical efficacy section of this report for a detailed discussion regarding the study designs and study populations of Study 102, 103 and 105.

Additional supportive data from Study 105 Cohort A1, and Phase 1 and 2 studies in patients and healthy volunteers revealed no new safety signals and are therefore not discussed separately.

Safety data related to patients who have tolerated ELX/TEZ/IVA in the 4-week run-in period. Furthermore, subjects who had a history of intolerance to ELX/TEZ/IVA or VNZ/TEZ/D-IVA that would pose an additional risk to the subject in the opinion of the investigator were not eligible to enrol in studies 102 and 103. Of note, the majority of subjects (86.3%) were using a CFTR modulator on or prior to informed consent. Data in CFTR modulator naïve patients is missing. Based on data from study 101 (19 patients at the dose corresponding to the Form D dose intended for marketing plus 20 patients at a higher dose) and data from pooled studies 102 and 103 (although patients were exposed to ELX/TEZ/IVA in the run-in period) do not suggest a different safety profile in CFTRm naïve patients.

*Exposure*

The size of the safety database and the length of follow-up is considered sufficient for this MAA. The number of patients exposed for a minimum of one year is substantially larger than the 100 patients recommended in the ICH Topic E. In the Pooled Safety Set in CF patients aged 12 years and older, the mean exposure was 49.5 weeks, and 293 patients received ≥52 weeks of treatment with VNZ/TEZ/D-IVA. However, this is limited to the maximum documented exposure of 54.1 weeks. A total of 136 (14.0%) subjects were aged 12 to <18 years of age, meeting PIP requirements. In Study Cohort B1, 78 CF patients aged 6 through 11 years received at least 1 dose of VNZ/TEZ/D-IVA in the Treatment Period, with a mean exposure of 23.8 weeks. A total of 29 patients received >24 weeks of treatment in this Cohort. Additional data will become available post-approval.

*Posology*

The posology used in studies 102 and 103 was VNZ 20mg, TEZ 100mg and D-IVA 250mg daily which is aligned with the proposed PI posology for ≥40kg. It is noted that within the pooled population of 102 and 103, there are some participants that had a weight of <40kg, minimum weight 32kg for ELX/TEZ/IVA and 33kg for VNZ/TEZ/D-IVA. The applicant provided an overview of treatment emergent AEs by weight for patients <40kg vs. ≥40kg. No new safety concerns were identified. The safety profile in the subgroup analyses is generally consistent with the overall safety findings. However, the small number of subjects with weight < 40kg is a limitation of this review. Continued monitoring of safety in patients with weight <40kg as part of routine pharmacovigilance and the Category 3 open label extension studies 104, 106 and the PASS included in the proposed post-authorisation PhV development plan are considered adequate to address the limitation of this review.

*Adverse events, serious adverse events and deaths*

Overall, VNZ/TEZ/D-IVA had a generally similar safety profile as ELX/TEZ/IVA based on the Pooled Safety Set with patients 12 years and older. Almost all patients experienced an AE (~96% in both arms) in the Pooled Safety Set, of which ~35% was considered at least possibly related. Severe AEs were reported for ~11% in both arms and SAEs in 14.2% of patients in the VNZ/TEZ/D-IVA arm vs. 16.5% in the ELX/TEZ/IVA arm. Related SAEs occurred in 1.5% vs. 2.6%, respectively. There were no deaths reported in the VNZ/TEZ/D-IVA clinical development programme during the TE Period. Both VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups from the Pooled Safety Set had a lower incidence of related AEs, SAEs and AEs leading to treatment interruption compared to the Studies 445-102 and 445-105 dataset in ELX/TEZ/IVA naïve patients.

When indirectly compared to the Pooled Safety Set in patients ≥12 years of age, paediatric patients 6 through 11 years of age in Study 105 Cohort B1 experienced AEs of lower severity. All AEs were mild or moderate in severity. The incidence of SAEs (7.7%) and overall incidence of AEs that led to either study drug interruption or study drug discontinuation (1.3% each) was low.

The most common AEs and SAEs throughout the clinical development programme were generally consistent with common manifestations of CF disease or with common illnesses in CF.-

In the Pooled Safety Set, there was a slightly higher incidence of AEs and SAEs of influenza in the VNZ/TEZ/D-IVA group compared to the ELX/TEZ/IVA group. All influenza events were assessed as unlikely related or not related and resolved with no change to study drug dosing. The overall incidence of the SOC of infections and infestations was balanced between the 2 groups (72.7% in the VNZ/TEZ/D-IVA group and 79.8% in the ELX/TEZ/IVA group). The incidence of infective PEx of CF and COVID-19 were slightly higher in the ELX/TEZ/IVA group. In OLE study 104, AEs of influenza were reported as well, including 1 related SAE.

An association with study drug cannot be fully ruled out. In line with ELX/TEZ/IVA, influenza has been added as common adverse reaction SmPC section 4.8 and reporting rates will be monitored in subsequent PSURs.

Most frequent related AEs were elevated transaminases, diarrhoea and headache, all of which occurred with slightly higher frequency in the VNZ/TEZ/D-IVA arm. Severe AEs occurred with similar frequencies in both treatment arms of the Pooled Safety Set (~11%), most frequently being infective PEx of CF (~3.8%).

Related SAEs occurred with low frequency (1.5% in the VNZ/TEZ/D-IVA arm vs. 2.6% with ELX/TEZ/IVA) in the Pooled Safety Set. The only related SAEs that were reported for more than 1 patient were transaminase elevations. In Study 105 Cohort B1, one (1.3%) patient had a SAE of constipation that was considered possibly related to study drug. Although some single SAEs were considered related to treatment by the investigator, detailed review of these cases indicated that relationship with VNZ/TEZ/D-IVA was unlikely for example due to pre-existing conditions.

*Adverse events of special interest*

- *Elevated transaminase* events are common in CF patients receiving IVA monotherapy, TEZ/IVA, and ELX/TEZ/IVA. In the Pooled Safety Set, the incidence of transaminase elevation AEs was slightly higher in the VNZ/TEZ/D-IVA group compared to the ELX/TEZ/IVA group. This imbalance was primarily observed during the first 3 months of treatment. An appropriate warning for elevated transaminases and hepatic injury is included in SmPC section 4.4.
- *Rash* occurred with slightly higher frequency in the VNZ/TEZ/D-IVA treatment group of the Pooled Safety Set compared to the ELX/TEZ/IVA treatment group (11% vs. 7.7%), primarily in the first month of treatment and with a higher incidence in females compared to males. The overall incidence is lower when indirectly compared to the Studies 445-102 and 445-105 52-week data. One event was serious and there were treatment interruptions (n=2) and discontinuations (n=1) due to rash. Rash is included as ADR in SmPC section 4.8 and in response to the list of questions, a warning regarding patients taking hormonal contraceptives who develop rash (i.e. to consider interrupting VNZ/TEZ/D-IVA and hormonal contraceptives) is included in section 4.4. This is in line with the product information of Kaftrio.
- *CK elevations* occurred with almost similar frequencies in both treatment arms of the Pooled Safety Set (~9%) and were mostly mild or moderate of severity. None of the subjects had AEs of rhabdomyolysis. Blood creatine phosphokinase increased is included as ADR in SmPC section 4.8, which is agreed. No further risk minimisation is considered warranted at present.
- *Hypoglycaemia* was reported for 1.7% of patients in the VNZ/TEZ/D-IVA group and 3.7% in the ELX/TEZ/IVA group. Almost all patients in the VNZ/TEZ/D-IVA group with a hypoglycaemia event (7/8) had a previous history of CF related diabetes and 3/8 were on insulin, none of the events were serious. The event rate with VNZ/TEZ/D-IVA was lower (1.80 events/100 PY) than the event rate in the ELX/TEZ/IVA group (4.27/100 PY) and (indirectly compared) pooled placebo data from other studies (4.82 events/100 PY). Altogether, it is unlikely that the hypoglycaemia events are related to VNZ/TEZ/D-IVA treatment.
- *Cataract* was reported with similar frequencies in both treatment arms of the Pooled Safety Set (0.6% vs. 0.8%). No visually significant AEs of cataract have been reported in this data set or Study 105 Cohort A1 or B1. As D-IVA is a deuterated isotopologue of IVA, it is agreed with the MAH that the potential risk of cataract is considered applicable to D-IVA containing regimen as well. As such, the

proposed warning in the SmPC and inclusion of cataract as potential serious risk in the RMP (in line with Ivacaftor and ELX/TEZ/IVA) are agreed.

- *Neuropsychiatric events* were reported with similar frequencies in both treatment arms of the Pooled Safety Set (~12%). The overall nature and frequency of these events were generally consistent with the background events in the CF population, which is known to have a high prevalence of mental health issues. However, in total 4.6% (n=22) of events in the VNZ/TEZ/D-IVA group were considered related to treatment by the investigator. Some of these events resolved without changes to study drug dosing (n=6 in Studies 102 and 103) and several patients had confounding psychosocial stressors and/or long latency (n=7 in Studies 102 and 103). Still, for several AEs relationship with treatment could not be ruled out. Moreover, in 2 patients with AEs of mental fatigue, depression, anxiety and insomnia de-challenge and/or rechallenge revealed at least a possible relationship with treatment. Based on all available evidence, depression and anxiety were considered at least possibly related to VNZ/TEZ/D-IVA treatment. In response to the list of questions, these ADRs have been reflected in the ADR table of SmPC section 4.8. In addition, an appropriate warning regarding depression (in line with the SmPC of ELX/TEZ/IVA) is included in SmPC section 4.4.

*Safety in special populations*

Subgroup analyses by age (≥12-<18 [n=136] vs. ≥18 [n=835]) of the Pooled Safety Set were generally consistent with overall safety results. The maximum age investigated in the Pooled Safety Set was 71.6 years. In the 2 patients aged ≥65 years treated with VNZ/TEZ/D-IVA, no SAEs or discontinuations were reported.

Subgroup analyses by sex, ppFEV1 at baseline, geographic region and prior CFTR modulator use were generally consistent with the overall safety profile in the Pooled Safety Set, no new safety signals were observed.

Phase 1 nonrandomised open-label Study 008 evaluated the PK, safety and tolerability of a single dose of VX-121/TEZ/D-IVA in subjects with moderate hepatic impairment (MHI). AEs and at least possibly related AEs were reported more frequently in subjects with MHI compared to healthy subjects, though all were of mild severity. There were no Grade 3+ AEs, SAEs or deaths. In SmPC section 4.2, use of VNZ/TEZ/D-IVA is not recommended in patients with moderate to severe hepatic impairment, which is agreed based on the limited data available in CF patients with hepatic impairment and frequent hepatic AEs.

No safety data is presented for patients with renal impairment. Due to the minimal renal clearance of VNZ, TEZ, and D-IVA, renal impairment is not expected to impact safety of VNZ/TEZ/D-IVA and it is therefore agreed that no dose adjustment is recommended in SmPC section 4.2.

*Discontinuations due to AEs*

The overall rates of treatment discontinuation due to AEs were similar (~3.8%) between treatment groups of the Pooled Safety Set. As expected, the most frequent AEs leading to treatment discontinuation and/or interruption were increases in liver enzymes.

*Long term safety data*

Interim long-term data for patients treated in the three pivotal studies is derived from ongoing OLE Studies 104 and 106. Overall, no new safety signals have emerged at the interim analyses. Both studies are included as Category 3 Post Authorisation Safety Study (PASS) in the RMP. Final reports are expected in March 2026 (Study 104) and April 2030 (Study 106).

Two neurologic events (AE of epilepsy and SAE of seizure) were reported in a paediatric patient that led to treatment discontinuation in OLE Study 106. For this patient an AE of seizure was reported in the parent Study 105 as well. The sponsor assessed the clinical course of the seizure events as most consistent with juvenile epilepsy given the age at onset and the occurrence of seizures off study drug, and therefore unlikely related to study drug. This is acknowledged.

*Laboratory values*

No clinically significant trend in laboratory assessments or vital signs were observed.

***Assessment of paediatric data on clinical safety***

Please refer to general discussion above. Presented data for the Pooled Safety Set of Study 102 and 103 reflect safety of VNZ/TEZ/D-IVA in patients 12 years and older. Study 105 Cohort B1 included CF patients 6 through 11 years of age.

### 2.5.10. Conclusions on clinical safety

By replacing ELX with VNZ and IVA with D-IVA, no additional safety concerns have been observed thus far. The safety profile of VNZ/TEZ/D-IVA is generally similar to ELX/TEZ/IVA based on available data for the Pooled Safety Set in patients 12 years and older. When indirectly compared to the Pooled Safety Set, the safety profile of paediatric patients 6 through 11 years of age in Study 105 Cohort B1 was generally similar although AEs were reported with lower severity.

## *2.6. Risk Management Plan*

### 2.6.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

**Table 47. Summary of safety concerns in proposed RMP**

| | |
|---|---|
| **Important identified risks** | • Hepatoxicity |
| **Important potential risks** | • Cataract |
| **Missing information** | • Use in pregnancy or breastfeeding<br>• Long-term safety<br>• Use in patients with moderate or severe hepatic impairment<br>• Use in children aged 6 to 11 years |

## 2.6.2. Pharmacovigilance plan

**Table 48. Planned and ongoing post-authorisation studies in the pharmacovigilance plan**

| Study/Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit-risk)** | | | | |
| **Post-authorisation Efficacy Study** (PAES)<br><br>Planned | To evaluate effectiveness / CF disease progression outcomes (including $ppFEV_1$, BMI, and SwCl), safety outcomes, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking VNZ/TEZ/D-IVA in the real-world setting | • Hepatotoxicity<br>• Use in pregnancy<br>• Long-term safety<br>• Use in patients with moderate or severe hepatic impairment<br>• Use in children aged 6 to 11 years | Annual Reports<br><br>Final Report | 31 December 2026/2027/2028/ 2029<br><br>31 December 2030 |
| **Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit-risk)** | | | | |
| Not applicable | | | | |
| **Category 3 – Required additional PV activities (by the competent authority)** | | | | |
| **Open-label extension study in CF subjects ages 12 years and older** (Study 104)<br><br>Ongoing | **Primary Objective**<br>• To evaluate the long-term safety and tolerability of VNZ/TEZ/D-IVA<br>**Secondary Objective**<br>• To evaluate the long-term efficacy of VNZ/TEZ/D-IVA | • Hepatotoxicity<br>• Cataract<br>• Long-term safety | 96 Week Report | 31 July 2026 |
| **Open-label extension study in CF subjects ages 1 to 11 years** (Study 106)<br><br>Ongoing | **Primary Objective**<br>• To evaluate the long-term safety and tolerability of VNZ/TEZ/D-IVA<br>**Secondary Objective**<br>• To evaluate the long-term efficacy of VNZ/TEZ/D-IVA | • Hepatotoxicity<br>• Cataract<br>• Long-term safety<br>• Use in children aged 6 to 11 years of age | 96 Week Report | 31 May 2030 |

BMI: body mass index; CF: cystic fibrosis; MA: market authorisation; PAES: post-authorisation efficacy study; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; PV: pharmacovigilance; Study 104: VX20-121-104; Study 106: VX22-121-106; SwCl: sweat chloride; TEZ: tezacaftor; VNZ/TEZ/D-IVA: vanzacaftor in combination with tezacaftor and deutivacaftor

## Risk minimisation measures

**Table 49. Summary of risk minimisation measures**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Hepatotoxicity** | **Routine risk minimisation measures:**<br>SmPC Sections 4.4 and 4.8<br>SmPC Section 4.4 where recommendations for LFT monitoring and treatment stopping rules are provided.<br>PL Sections 2 and 4<br>PL Sections 2 and 4 where expectations for LFT monitoring and detection of potential signs of liver problems are discussed.<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>• Open-label extension study in CF subjects ages 12 years and older (Study 104) (96 Week Report: 31 July 2026)<br>• Open-label extension study in CF subjects ages 1 to 11 years of age (Study 106) (96 Week Report: 31 May 2030)<br>• PASS (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030) |
| **Cataract** | **Routine risk minimisation measures:**<br>SmPC Sections 4.4 and 5.3<br>SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided.<br>PL Section 2<br>PL Section 2 where expectations for eye examinations are discussed.<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>• Open-label extension study in CF subjects ages 12 years and older (Study 104) (96 Week Report: 31 July 2026)<br>• Open-label extension study in CF subjects ages 1 to 11 years of ages (Study 106) (96 Week Report: 31 May 2030) |
| **Use in pregnancy or breastfeeding** | **Routine risk minimisation measures:**<br>SmPC Sections 4.6 and 5.3<br>SmPC Section 4.6 where advice is given regarding use during pregnancy and breastfeeding.<br>PL Section 2<br>PL Section 2 where advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding.<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Pregnancy follow-up questionnaire<br><br>**Additional PV activities:**<br>• PASS (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030) |

**Table 49. Summary of risk minimisation measures**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Long-term safety** | **Routine risk minimisation measures:**<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>• Open-label extension study in CF subjects ages 12 years and older (Study 104) (96 Week Report: 31 July 2026)<br>• Open-label extension study in CF subjects ages 1 to 11 years of age (Study 106) (96 Week Report: 31 May 2030)<br>• PASS (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030) |
| **Use in patients with moderate or severe hepatic impairment** | **Routine risk minimisation measure:**<br>SmPC Sections 4.2 and 5.2<br>SmPC Sections 4.2 where recommendations regarding use in patients with hepatic impairment are provided.<br>PL Sections 2 and 3<br>PL Sections 2 and 3 where advice to speak with a healthcare professional before use in patients with liver problems is provided.<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>• PASS (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030) |
| **Use in children aged 6 to 11 years** | **Routine risk minimisation measure:**<br>SmPC Sections 4.1, 4.2, and 4.8<br>PL Sections 1 and 2<br>Prescription only<br><br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>• Open-label extension study in CF subjects ages 1 to 11 years of ages (Study 106) (96 Week Report: 31 May 2030)<br>• PASS (Annual Reports: 31 December 2026/2027/2028/2029; Final Report: 31 December 2030) |

CF: cystic fibrosis; LFT: liver function test; PL: Package Leaflet; PV: pharmacovigilance; PASS: post-authorisation safety study; Study 104: VX20-121-104; Study 106: VX22-121-106; SmPC: Summary of Product Characteristics; TEZ: tezacaftor

## 2.6.3. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

## *2.7. Pharmacovigilance*

### 2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20 December 2024.The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

## *2.8. Product information*

### 2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.8.2. Additional monitoring

- Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Alyftrek (Deutivacaftor / Tezacaftor / Vanzacaftor) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU; It has a PAES imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)].

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. Cystic fibrosis is caused by mutations in the CFTR gene that result in absent or deficient function of the CFTR protein at the cell surface. The CFTR protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF. Lung disease is the primary cause of morbidity and mortality in people with CF.

F508del, is the most common disease-causing mutation. About 50% of the CF population is homozygous for the F508del mutation, while this allele is present in about 80% of the overall CF population. People with CF who do not carry at least one F508del mutation are rare and have CFTR mutations that are individually rare. Patients without non-F508del mutation represent about 20% of the total CF population, including those patients that are homozygous for minimal function mutations (MF/MF). MF mutations are not responsive to modulator therapy.

The current application refers to a new fixed combination medicinal product including 3 orally administered CFTR modulators , vanzacaftor, tezacaftor and deutivacaftor, (VNZ/TEZ/D-IVA) that work by improving activity of CFTR protein in the lungs. Treatment is expected to thick the abnormal secretions, reduce symptoms of the disease, and improve lung function.

This new fixed combination shows important similarities with ELX/TEZ/IVA. Compared to ELX/TEZ/IVA, the ELX component has been replaced by VNZ. D-IVA is a deuterated isotopologue of ivacaftor with a similar chemical structure with comparable PD properties. D-IVA is administered in a higher dose than IVA, and this product can be administered once daily compared with currently approved modulator treatments administered twice daily.

The initially claimed indication was as follows: Alyftrek is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see section 5.1, Table 4).

This indication was updated during the procedure to seek the identical broader indication as Kaftrio/Kalydeco recently authorised by CHMP as follows:

Alyftrek tablets are indicated for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2 and 5.1).

### 3.1.2. Available therapies and unmet medical need

Existing CF treatments can be broadly classified in 2 groups:
(1) therapies that manage the symptoms, complications, and comorbidities of the disease (e.g., antibiotics,

mucolytics, pancreatic enzyme replacement therapy), and
(2) CFTR modulators (i.e., correctors and potentiators) that target the underlying cause of the disease.

Modulators have gained an important place in the treatment of CF. They have been shown to have systemic benefit in CF disease with long-term treatment for individuals by improving lung function and quality of life. The most effective CFTR modulator with the broadest indication to date is the triple combination Kaftrio (ELX/TEZ/IVA), which is indicated in people with CF who harbour an F508del mutation. A new variation for Kaftrio has just been approved (EMEA/H/C/005269/WS2551) for all CF patients who do not have two class I mutations.

### 3.1.3. Main clinical studies

The main evidence of efficacy and safety was obtained from two pivotal phase 3 trials. Both trials investigated the triple combination vanzacaftor20 mg qd/tezacaftor 100 mg qd/deutivacaftor 250 mg qd in comparison to the approved triple combination elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h.

The trials had a similar design being a 52-week, randomised, double-blind, active-controlled, parallel-group study in CF patients 12 years and older, but included a different population based on the CFTR genotype.

Study 102 enrolled subjects heterozygous for the F508del-CFTR mutation and a minimal function mutation (defined as a Class I minimal function mutation) (F/MF). A total of 398 subjects received at least one dose of study drug.

Study 103 enrolled subjects homozygous for F508del (F/F), F508del and a residual function mutation (F/RF), F508del and a gating mutation (F/G), and triple combination responsive CFTR mutation and no F508del mutation (TCR/non-F) genotypes. TCR mutations were defined as 1 of 178 ELX/TEZ/IVA-responsive mutations indicated for Kaftrio in the US based on *in vitro* data using the FRT system. A total of 573 subjects received at least one dose of study drug.

The primary endpoint was absolute change from baseline in ppFEV1, accompanied by key secondary endpoints of absolute change from baseline in sweat chloride (SwCl) levels and the proportion of subjects who obtained SwCl levels <60 mmol/L and <30 mmol/L. The primary endpoint was tested for non-inferiority, whereas the key secondary endpoints were tested for superiority. For the proportions of subjects who obtained SwCl levels <60 mmol/L and <30 mmol/L, data from Studies 102 and 103 were pooled. Proportions for each study separately were included as secondary endpoints.

Supportive efficacy and safety data were obtained from an open-label study (study 105) in children aged 6-11 years with at least one TCR mutation (TCR/any). A total of 78 subjects received at least one dose of study drug. Secondary efficacy endpoints were absolute change from baseline in SwCl and ppFEV1 and the proportion of subjects who obtained SwCl levels <60 mmol/L and <30 mmol/L.

Additional supportive data are provided with the Alyftrek responsive mutations on the *in vitro* FRT test.

## *3.2. Favourable effects*

*CF patients 12 years and older with an F/MF genotype (study 102)*

From a baseline established on ELX/TEZ/IVA in the run-in period, when patients were followed up regardless of treatment discontinuation or use of another CFTR-modulator for at least 3 days (primary estimand), the

difference in the absolute change from baseline in ppFEV1 through Week 24 was 0.2 percentage points (95% CI: -0.7, 1.1) between VNZ/TEZ/D-IVA and ELX/TEZ/IVA. Under the supplemental hypothetical estimand strategy (i.e., targeting the effect had patients continued allocated treatment and not used another CFTR-modulator for at least 3 days) the difference in the absolute change from baseline in ppFEV1 through Week 24 was also estimated to be 0.2 percentage points (95% CI: -0.7, 1.1).

Treatment with VNZ/TEZ/D-IVA resulted in a statistically significant greater reduction in SwCl from baseline through week 24 compared to ELX/TEZ/IVA, with an LS mean treatment difference of -8.4 mmol/L (95% CI: -10.5, -6.3).

Subgroup analyses were consistent with the result from the primary analysis, namely, that regardless of differences in age, ppFEV1 at baseline, SwCl at baseline, sex, and geographic region, subjects in the VNZ/TEZ/D-IVA group had similar improvements in ppFEV1 compared to subjects in the ELX/TEZ/IVA group. No subgroup analyses were performed for the key secondary endpoints.

*CF patients 12 years and older with an F/F, F/G, F/RF, or TCR/non-F genotype (study 103)*

From a baseline established on ELX/TEZ/IVA in the run-in period, when patients were followed up regardless of treatment discontinuation or use of another CFTR-modulator for at least 3 days (primary estimand), the LS mean treatment difference was 0.2 percentage points (95% CI: -0.5, 0.9). For the supplemental estimand strategy, the LS mean treatment difference was 0.3 percentage points (95% CI: -0.4, 1.0).

Treatment with VNZ/TEZ/D-IVA resulted in a statistically significant greater reduction in SwCl from baseline through week 24 compared to ELX/TEZ/IVA, with an LS mean treatment difference of -2.8 mmol/L (95% CI: -4.7, -0.9).

Subgroup analyses were consistent with the results from the primary analysis, namely, that regardless of differences in age, ppFEV1 at baseline, SwCl at baseline, sex, geographic region, and genotype subgroup, subjects in the VNZ/TEZ/D-IVA group had similar effects in ppFEV1 compared to subjects in the ELX/TEZ/IVA group. No subgroup analyses were performed for the key secondary endpoints.

*Pooled analysis (Studies 102 and 103)*

Based on pooled data from Studies 102 and 103, the estimated odds ratio for the proportion of subjects with SwCl <60 mmol/L through week 24 was 2.21 (95% CI: 1.55, 3.15). The estimated odds ratio for the proportion of subjects with SwCl <30 mmol/L through Week 24 was 2.87 (95% CI: 2.00, 4.12).

*CF patients 6-11 years of age with a TCR/any genotype (Study 105)*

Following baseline established on ELX/TEZ/IVA in CF subjects 6-11 years, lung function was normal with a mean (SD) ppFEV1 of 99.7 (15.1) percentage points. Treatment with VNZ/TEZ/D-IVA maintained this benefit in ppFEV1, with an LS mean change from baseline through Week 24 of 0.0 percentage points (95% CI: -2.0, 1.9).

Treatment with VNZ/TEZ/D-IVA further lowered SwCl levels from ELX/TEZ/IVA baseline through week 24 by an LS mean (SD) change of -8.6 (1.2) mmol/L.

The proportion of subjects with SwCl <60 mmol/L through week 24 was 94.9% (95% CI: 87.4%, 98.6%). The proportion of subjects with SwCl <30 mmol/L through week 24 was 52.6% (95% CI: 40.9%, 64.0%). These proportions were 83.3% and 39.0% at ELX/TEZ/IVA baseline, respectively.

## 3.3. Uncertainties and limitations about favourable effects

*Pivotal studies*

The responder rate in the outcome parameter SwCl <30 mmol/L and SwCl <60 mmol/L is a supportive and secondary endpoint. It is not an established clinical efficacy outcome established for surrogacy and has not been prospectively validated across different classes.

Non-F508del mutations: Supportive clinical data for the non-F508del population is restricted to a total of 20 mutations.

No clinical data are available for a large number of rare CFTR mutations. Similarly, data from the *in vitro* FRT assay are not (yet) available for very rare mutations.

*Paediatric subjects*

Study 105 was a single arm trial and efficacy was only assessed as secondary endpoints. Data are limited due to the low number of enrolled subjects (n=78) with most (n=61) having either F/F or F/MF genotype. No data have been provided on the RF genotype. Only 6 subjects had no F508del mutation.

## 3.4. Unfavourable effects

TEAEs were reported for nearly all patients (~96%) in the VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups of the Pooled Safety Set (based on studies 102 and 103 in patients ≥12 years of age), as well as Study 105 Cohort B1 in patients 6-11 years of age. The most common TEAEs were infective PEx of CF, cough, and upper respiratory tract infection. One TEAE occurred in ≥10% of patients in the Pooled Safety Set and with >3% higher incidence in the VNZ/TEZ/D-IVA arm: influenza (10.8% vs. 5.3%).

Related TEAEs were reported for ~35% of patients in both treatment arms of the Pooled Safety Set. Based on individual study reports, most frequent related AEs were elevated transaminases, diarrhoea and headache, all of which occurred with slightly higher frequency in the VNZ/TEZ/D-IVA arm. For patients 6 through 11 years of age in Study 105 Cohort B1, 29.5% related TEAEs were reported, most frequently being headache, ALT increased, neutrophil count decreased, cough and rash.

Grade 3 or higher AEs were reported for ~11% of patients in both treatment arms of the Pooled Safety Set. Severe AEs occurring in more than 2 patients were infective PEx of CF (3.8% vs. 3.5%, respectively), influenza (0.8% vs. 0.4%), ALT increased (0.8% vs. 0.2%), migraine (0.6% vs. 0%), and haemoptysis (0.6% vs. 0.2%). No Grade 3 or higher TEAEs were reported in Study 105 Cohort B1.

SAEs were reported for 14.2% of patients in the VNZ/TEZ/D-IVA arm vs. 16.5% in the ELX/TEZ/IVA arm of the Pooled Safety Set and 7.7% in Study 105 Cohort B1. SAEs occurring in >2 patients in the VNZ/TEZ/D-IVA arm were: infective PEx of CF (6.0% vs. 7.1%), influenza (1.5% vs. 0.6%), pneumonia (0.8% vs. 1.2%) and haemoptysis (0.6% each). In Study 105 Cohort B1, 6 (7.7%) patients had at least 1 SAE. One SAE occurred in more than 1 subject: infective PEx of CF (2 [2.6%] patients).

Related SAEs were reported for 1.5% vs. 2.6% of patients, respectively in the Pooled Safety Set. Related SAEs occurring in more than 2 patients were ALT and AST increased (0.4% vs. 0.4 % and 0.4% vs. 0.2%, respectively). In Study 105 Cohort B1, one (1.3%) patient had an SAE of constipation that was considered possibly related to study drug.

AESIs:

- *Transaminase elevations* were reported for 9% vs. 7.1% of patients in the Pooled Safety Set. This led to study discontinuation in 1.5% vs. 0.6% of patients. Two patients had a serious elevated transaminase event. In Study 105 Cohort B1, 5.1% of patients had at least 1 elevated transaminase event, none of which were serious or led to treatment discontinuation or interruption.
- *Rash* was reported for 11% vs. 7.7% of patients in the Pooled Safety Set, primarily in the first month of treatment and with a higher incidence in females compared to males (13% vs. 9.4%) in the VNZ/TEZ/D-IVA arm. There were no serious events and 1 led to study treatment discontinuation. In Study 105 Cohort B1, 5.1% of patients had at least 1 rash event, all of mild severity and none led to treatment discontinuation or interruption.
- *CK elevations* occurred in 9% of both treatment arms in the Pooled Safety Set, with 1 of the events in each arm being serious. Both led to treatment discontinuation. None of the subjects had AEs of rhabdomyolysis. In Study 105 Cohort B1, 2.6% of patients had at least 1 CK elevation event, both of mild severity and not leading to treatment discontinuation or interruption.
- *Hypoglycaemia* evens were reported for 1.7% vs. 3.7% of patients in the Pooled Safety Set, there were no serious events or events leading to treatment discontinuation or interruption. There were no events in Study 105 Cohort B1.
- *Cataract* was reported with similar frequencies in both treatment arms of the Pooled Safety Set (0.6% vs. 0.8%) and for 1 (1.3%) patient in Study 105 Cohort B1. No visually significant AEs of cataract have been reported in this study or the Pooled Safety Set.
- *Neuropsychiatric events* were reported in 11.5% vs. 12% of patients in the Pooled Safety Set, most frequently being anxiety (4.4% vs. 2.0%), insomnia (3.1% vs. 4.5%) and depression (2.9% vs. 2.0%). Serious events occurred in 0.8% of patients in each treatment group, and treatment was discontinued due to neuropsychiatric events in 0.6% vs. 0.4% of patients. In Study 105 Cohort B1, 4 (5.1%) patients had at least 1 neuropsychiatric event, all of mild severity and none leading to treatment discontinuation or interruption.

Discontinuations due to AEs were reported for ~3.8% of patients in both treatments arm of the Pooled Safety Set. The most frequent AEs leading to discontinuation of treatment were ALT and AST increased (1.5% vs. 0.6% and 1.3% vs. 0.6%, respectively). In Study 105 Cohort B1, 1 (1.3%) patient had mild, possibly related AEs of cough and fatigue that led to treatment discontinuation.

Treatment interruptions due to AEs were reported for 2.4% vs. 4.2% of patients in the Pooled Safety Set, mostly due to transaminase elevations. In Study 10 Cohort B1, 1 patient had a seizure (moderate severity, possibly related to study drug) that resulted in study drug interruption for 1 Day.

Long-term interim safety data from OLE Study 104 (rollover from Studies 102 and 103) showed that 14.2% of patients experienced an SAE, with 0.5% being related to treatment. In 106 (rollover from Study 105) this was 12% and 1.3%, respectively. The most frequent SAE was infective Pulmonary exacerbation (PEx) of CF (~2%) in both studies. Treatment discontinuation was reported in 2.2% of patients in Study 104 and 2.7% in Study 106.

In case of the proposed dose recommendations when given with strong or moderate inhibitors of CYP3A, exposure of TEZ is lower than that observed when a normal dose is administered in the absence of an inhibitor of CYP3A.

## 3.5. Uncertainties and limitations about unfavourable effects

- Data in CFTR modulator treatment naïve patients is missing. Furthermore, subjects who had a history of intolerance to ELX/TEZ/IVA or VNZ/TEZ/D-IVA were not eligible to enrol in studies 102 and 103. The overall safety experience is still limited in CF subjects 6 through 11 years of age. These patients were evaluated in Study 105 which had a relatively small sample size of 95 subjects (17 subjects in Cohort A1 and 78 subjects in Cohort B1).
- Although no new safety concerns were identified in an interim analysis of OLE studies 104 and 106, long term safety data remains limited in adults and even more in the paediatric population.).

## 3.6. Effects Table

**Table 50. Effects table for VNZ/TEZ/D-IVA in the treatment of CF in people aged 6 years and older who have at least one F508del mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (data cut-off: 30 November 2023).**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| **CF patients with F/MF genotype** | | | | | | |
| | | | VNZ/TEZ/D-IVA | ELX/TEZ/IVA | | |
| ppFEV1 0-24 weeks | Absolute change from baseline# | % | 0.5 (-0.1, 1.1) | 0.3 (-0.3, 0.9) | | 1 |
| SwCl 0-24 weeks | Absolute change from baseline# | mmol/L | -7.5 (-6.0, -9.0) | 0.9 (-0.6, 2.3) | Statistically significant difference, clinical relevance undetermined | 1 |
| **CF patients with F/F, F/G, F/RF, or TCR/non-F genotype** | | | | | | |
| ppFEV1 0-24 weeks | Absolute change from baseline# | % | 0.2 (-0.3, 0.7) | 0.0 (-0.5, 0.5) | | 2 |
| SwCl 0-24 weeks | Absolute change from baseline# | mmol/L | -5.1 (-6.4, -3.7) | -2.3 (-3.6, -0.9) | Statistically significant difference, clinical relevance undetermined | 2 |
| **Paediatric CF patients with TCR/any genotype** | | | | | | |
| ppFEV1 0-24 weeks | Absolute change from baseline# | % | 0.0 (-2.0, 1.9) | | No comparator arm | 3 |

| | | | | | | |
|---|---|---|---|---|---|---|
| SwCl 0-24 weeks | Absolute change from baseline[#] | mmol/L | -8.6 (-11.0, -6.3) | | No comparator arm | 3 |
| **Unfavourable Effects** | | | | | | |
| TEAEs | Proportion of patients<br><br>*Infective PEx of CF**<br>*Cough*<br>*COVID-19*<br>*Nasopharyngitis*<br>*Influenza* | % | 95.6%<br><br>27.7%<br><br>22.5%<br>22.3%<br>21.3%<br><br>10.8% | 95.5%<br><br>32.2%<br><br>20.6%<br>25.9%<br>19.3%<br><br>5.3% | No new safety concerns identified in patients 6-11 years based on Study 105 Cohort B1.<br>Data in CFTR modulator treatment naïve patients is missing. | 4 |
| Related TEAEs | Proportion of patients | % | 35.0% | 35.6% | | 4 |
| SAEs | Proportion overall<br>Proportion related | % | 14.2%<br>1.5% | 16.5%<br>2.6% | | 4 |
| AEs leading to discontinuation | Proportion of patients | % | 3.8% | 3.7% | | 4 |

Abbreviations: AE: adverse event; CFTRm: CFTR modulator; D-IVA: deutivacaftor; ELX: elexacaftor; F/F: homozygous for F508del; F/G: heterozygous for F508del and a gating mutation; F/MF: heterozygous for F508del and a minimal function mutation; F/RF: heterozygous for F508del and a residual function mutation; IVA: ivacaftor; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TCR/non-F: heterozygous for a triple combination responsive mutation and no F508del mutation; TEZ: tezacaftor; VNZ: vanzacaftor; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Notes: 1 refers to Study 102; 2 refers Study 103; 3 refers to Study 105; 4 refers to the Pooled Safety Set; [#] Baseline value was established while on ELX/TEZ/IVA treatment; * Most frequent TEAEs or with >3% higher incidence in the VNZ/TEZ/D-IVA arm.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

*CF patients 12 years and older with an F508del mutation*

In the clinical data, the F508del mutation was present in ~95% of the study populations of studies 102, 103, and 105 combined. Study 102 only included patients with the F/MF phenotype. A class I MF mutation results in no protein, implying that any effect found in study 102 can be fully attributed to the F508del allele. In

addition, 92.7% (study 103) and 92.3% (study 105) of the study population carried at least one F508del allele. Therefore, the clinical outcomes observed in the VNZ/TEZ/D-IVA development programme can largely be attributed to effects on the F508del allele targeting potentially ~80% of pwCF.

The pivotal clinical studies 102 (F/MF) and 103 (F/F, F/RF, F/G and TCR/non-F) showed no difference in lung function (ppFEV1) between Alyftrek and Kaftrio through 24 weeks of treatment. Study 102 demonstrated the efficacy for the F mutation as the MF mutation will not respond, the F/F, F/RG and F/G data provide supportive evidence for the efficacy in pwCF who harbour at least one F mutation. The chosen non-inferiority margin of 3% is considered acceptable, since treatment effects of at least 7% (lower bound of 95% CI) have been reported in Kaftrio development programmes, while the constancy of the trial design has been sufficiently justified.

Differences in the size of the effect on SwCl were observed in studies 102 and 103, with a more pronounced effect of VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA on the F/MF subjects in study 102 than on the heterogeneous study population of study 103. However, the clinical relevance of this difference has not been established. These key secondary outcomes on this pharmacodynamic endpoint support the results of the primary endpoint.

*CF patients 12 years and older with a TCR mutation and no F508del mutation*

In study 103, a total of 42 subjects with the TCR/non-F genotype were included, and within this subgroup, 22 TCR mutations were represented including 2 non CF causing mutations. In study 105, only 6 subjects without F508del allele were included, harbouring a total of 5 TCR (non-F) mutations, all of which also were represented in study 103. Two of these TCR mutations have been identified as non-CF-causing and should thus be excluded.

Clinical data in TCR/non-F patients are therefore very limited. Nevertheless, the applied broad application can be supported, considering that:

- Consistency of results for various subgroups (F/F, F/RF, F/G and TCR/non-F). Indeed, the subgroup of TCR/non-F showed comparable results for ppFEV1 and SwCl as the primary analyses.
- The indication is also supported with *in vitro* FRT data. The recently concluded WS5221 procedure (extension of indication) for Kaftrio provided sufficient evidence that a positive FRT response is indicative of a clinical response to Kaftrio. Kaftrio and Alyftrek essentially only differ in the VNZ and ELX component, while VNZ and ELX have comparable binding sites on the CFTR protein. Consistency between Kaftrio and Alyftrek has been demonstrated in obtained clinical and *in vitro* results. Based on these considerations, it is agreed that an observed response to Kaftrio would also result in a clinical response to Alyftrek.

*Paediatric CF patients (6-11 years of age)*

Study 105 provided supportive efficacy data in paediatric subjects with mostly either an F/F or F/MF genotype (78% of study population). SwCl levels in children were lower than those in adults and adolescents both at ELX/TEZ/IVA baseline and after 24 weeks of VNZ/TEZ/D-IVA treatment. This is in line with literature that SwCl levels slightly increase with age.

Other efficacy results including lung function are generally consistent with those of Studies 102 and 103, generally posing no efficacy issues regarding extrapolation of results in subjects ≥12 years towards children aged 6-11 years. The efficacy and safety data in the paediatric patients remains limited and will need to be further characterised in the post approval setting.

*Safety*

By replacing ELX with VNZ and IVA with D-IVA, no additional safety concerns have been observed thus far. The safety profile of VNZ/TEZ/D-IVA is generally similar to ELX/TEZ/IVA based on available data for the Pooled Safety Set in patients 12 years and older. The provided data is based on patients that could tolerate ELX/TEZ/IVA, while data obtained treatment naïve patients is limited.

The most common AEs and SAEs throughout the clinical development programme were generally consistent with common manifestations of CF disease or with common illnesses in CF. Discontinuations due to AEs were reported in a low proportion of patients (~3.8% of patients in both arms of the Pooled Safety Set), mainly due to elevated transaminases. Most frequent related AEs were elevated transaminases, diarrhoea and headache. Severe AEs occurred with similar frequencies in both treatment arms of the Pooled Safety Set (~11%), most frequently being infective PEx of CF (~3.8%). Related SAEs occurred with low frequency (1.5% in the VNZ/TEZ/D-IVA arm vs. 2.6% with ELX/TEZ/IVA) and the only related SAEs that were reported for more than 1 patient were transaminase elevations. Transaminase elevations and rash were the only AESIs that occurred with slightly higher frequency in the VNZ/TEZ/D-VA arm. This is reflected in the proposed SmPC. When indirectly compared to the Pooled Safety Set, the safety profile of paediatric patients 6 through 11 years of age in Study 105 Cohort B1 was generally similar although AEs were reported with lower severity.

Long term safety data remains limited. Final results of the OLE study will become available post-approval and reported for assessment (category 3 PASS).

With the approval of Kaftrio, it will be hard to collect additional efficacy and safety clinical data outside of RWD studies (e.g. registries) to support the various mutations in the non-F508del population, considering that this population is rare and genetically very heterogeneous. However, the level of uncertainties and current knowledge on the treatment response with VNZ/TEZ/D-IVA is greater than with ELX/TEZ/IVA. Therefore a post-authorisation efficacy and safety study  is requested by CHMP subject to Annex II condition.

The applicant has committed to provide additional supportive clinical efficacy data ($ppFEV_1$) through the proposed PAES (VX24-121-107) for all patients with CF who have 2 non-*F508del* mutations. In order to further characterise the efficacy and safety of deutivacaftor/tezacaftor/vanzacaftor in the treatment of cystic fibrosis in people aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene including people who have two non-F508del mutations (e.g. *N1303K*, non-canonical splice, and mutations supported by FRT data only), the MAH should conduct and submit the results of a non-interventional study based on data from a patient registry, according to an agreed protocol.
The applicant should pay special attention to patients with N1303K mutation and patients with non-canonical splice mutations. All efforts should be made to recruit these patients to the study and collect their efficacy data. Targets for recruitment of this group of patients should be prespecified in the study protocol.
This study will evaluate outcomes in the 5-year periods before and after treatment initiation with VNZ/TEZ/D-IVA, with 5 annual analysis reports planned to be submitted from 2026 through 2030. In addition to safety endpoints, this study will evaluate disease progression endpoints, including ppFEV1, BMI, and SwCl.

The group of patients with significant disease progression  should be analysed and their underlying mutation discussed.

Once more data on the use of VNZ/TEZ/D-IVA are generated, it will become possible to analyse the discriminatory statistics of the FRT assay for VNZ/TEZ/D-IVA with better precision. The applicant should

present this analysis together with each annual report submitted for the post-authorisation study to get confirmation that reliance on the FRT assay is appropriate for VNZ/TEZ/D-IVA.

A letter of commitment has been provided accordingly by the applicant.

### 3.7.2. Balance of benefits and risks

The benefit-risk balance is positive for patients homozygous and heterozygous for the F508del mutation, as well as for patients with a TCR mutation and no F508del mutation (homozygous non-F508del). Sufficient justification has been provided for the extrapolation of data from other CFTR modulators (Kaftrio, Symkevi, Kalydeco) to Alyftrek. The extrapolation is also supported by clinical and *in vitro* FRT data provided for Alyftrek.

Consequently, it is agreed that the same broad indication can be applied to Alyftrek as has been recently approved for Kaftrio, i.e., "the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least 1 non-class I mutation in the CFTR gene".

However, since the level of uncertainties in respect to the potential treatment response is greater with Alyftrek than with Kaftrio, the post-authorisation study for Alyftrek should be subject to Annex II condition.

## *3.8. Conclusions*

The overall benefit-risk balance of Alyftrek is positive for CF patients who have at least 1 non-class I mutation in the CFTR gene is positive, subject to the conditions stated in section 'Recommendations'.

# 4. Recommendations

***Similarity with authorised orphan medicinal products***

The CHMP by consensus is of the opinion that Alyftrek is not similar to Kaftrio or Symkevi within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity assessment.

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Alyftrek is favourable in the following indication:

> *Alyftrek tablets are indicated for the treatment of cystic fibrosis (CF) in people aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see sections 4.2 and 5.1).*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measure. The measure is a post-authorisation efficacy study (PAES) in accordance with the Commission Delegated Regulation (EU) No 357/2014 :

| **Description** | **Due date** |
|---|---|
| **Post-authorisation efficacy study (PAES)** (VX24-121-107) :<br>In order to further characterise the efficacy and safety of deutivacaftor/tezacaftor/vanzacaftor in the treatment of cystic fibrosis in people aged 6 years and older who have at least one non-Class I mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene including people who have two non-F508del mutations (e.g. *N1303K*, non-canonical splice, and mutations supported by FRT data), the MAH should conduct and submit the results of a non-interventional study based on data from a patient registry, according to an agreed protocol. | Final CSR<br>December 2030 |

***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States***

Not applicable.

***New Active Substance Status***

Based on the CHMP review of the available data, the CHMP considers that deutivacaftor/tezacaftor/vanzacaftor is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

***Paediatric Data***

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-003052-PIP01-21 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.