Amsterdam, 30 April 2020
EMA/273575/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Kalydeco

International non-proprietary name: IVACAFTOR

Procedure no.: EMEA/H/C/002494/P46 029

Note

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

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Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomic class
BMI	body mass index
CDC	Center for Disease Control and Prevention
CF	cystic fibrosis
CFTR	CF transmembrane conductance regulator protein
CFTR	*CF transmembrane conductance regulator gene*
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CI	confidence interval
CPK	creatine phosphokinase
CRF	case report form
CT	computed tomography
CYP	cytochrome P450
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
FAS	full analysis set
FDA	Food and Drug Administration
$FEF_{25-75\%}$	forced expiratory flow at 25-75% of the pulmonary volume
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
HR	heart rate
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IV	intravenous
IVA	ivacaftor
KM	Kaplan-Meier
LDCT	low-dose computed tomography
LFT	liver function test
LLN	lower limit of normal
LS	least square

LSM	least squares mean
LUM	lumacaftor
MCID	minimum clinically important difference
MedRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
PE	physical examination
PEx	pulmonary exacerbation
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	preferred term
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Friderica's formula
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SF-36	36-Item Short Form Survey
SI	SI units (International System of Units)
SOC	system organ class
SOP	standard operating procedure
TE	Treatment Emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

1. Introduction

VX16-770-127 (Study 127) is submitted as a stand-alone post-authorization measure (PAM) under Article 46 of Regulation (EC) No 1901/2006 (the "Paediatric Regulation").

Study 127 was designed to evaluate the efficacy of ivacaftor (IVA) treatment in subjects with cystic fibrosis (CF) 6 years of age and older who have a 3849 + 10KB C→T or D1152H-CFTR mutation.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Kalydeco tablets contains ivacaftor an orally administered CFTR potentiator that increases the channel open probability of CFTR protein at the cell surface to enhance chloride transport. In the EU, Kalydeco is authorised for the treatment of CF in patients aged 6 years and older and weighing 25 kg or more who have 1 of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.

Kalydeco is also approved for the treatment of CF in patients aged 18 years and older with an *R117H*-CFTR mutation.

In combination with tezacaftor, Kalydeco is authorised in patients with CF aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

Vertex initiated a phase 3b efficacy trial (study 127) in CF subjects 6 years of age and older, who have a 3849 + 10KB C→T or D1152H-CFTR mutation. It was performed at a single site in Israel.

Study 127 is a randomized, double-blind, placebo-controlled, crossover study to evaluate the efficacy of IVA in subjects with CF who are 6 years of age and older and have either a 3849 + 10KB C→T or D1152H-CFTR mutation.

The primary endpoint of study 127 was change from baseline in lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value ($LCI_{2.5}$), which is a measure of ventilation inhomogeneity. Additional efficacy endpoints included change from baseline in number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value (LCI5.0), sweat chloride, percent predicted forced expiratory volume in 1 second (ppFEV1), and Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score. The effect of ivacaftor on organoids carrying either 3849 + 10KBC→T or D1152H-CFTR mutations was also assessed.

Safety was assessed in terms of the following safety and tolerability assessments: treatment emergent adverse events (TEAEs), clinical laboratory values (liver function, amylase, lipase), vital signs, physical examinations (PEs), and ophthalmological examination (OEs; for subjects <18 years of age).

Study VX12-770-113 and Study VX14-661-108 demonstrated improvements with IVA treatment in subjects with residual CFTR function, and subjects who had a 3849 + 10KB C→T or D1152H-CFTR mutation were among those included in these studies. Study 127 only included subjects who have a 3849 + 10KB C→T or D1152H-CFTR mutation in order to evaluate the effects of IVA specifically in subjects with these 2 mutations.

2.2. Information on the pharmaceutical formulation used in the study

No new paediatric formulation was evaluated in Study 127. The test product was the same as the commercially approved product, Kalydeco, for patients 6 years of age and older (IVA 150-mg film-coated tablets). The test product was administered to study subjects orally at a dose of 150-mg (or matching placebo) q12h, which is also the commercially approved dose of Kalydeco.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for VX16-770-127: A Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy of Ivacaftor in Subjects with Cystic Fibrosis Who are 6 Years of Age and Older and Have Either a 3849 + 10KB C→T or D1152H-CFTR Mutation.

The 3849 + 10KB C→T CFTR mutation results in a partially active splice site in intron 19 that leads to the insertion of a new 84 base pair exon, which contains an in-frame stop codon between exon 19 and 20. This mutation has a prevalence of 0.2% to 2% and it results in a reduced amount of normal CFTR protein at the cell surface (average sweat chloride 66 mEq/L). The 3849+10kbC->T mutation leads to abnormal mRNA; however, a small amount of normally spliced transcripts can also be detected. The presence of these small amounts of normal cystic fibrosis transmembrane receptor protein in these cystic fibrosis patients is likely to be responsible for the milder severity of disease and a better life expectancy. It is expected to result in CF when combined with another CF-causing variant.

D1152H is a missense mutation that results in normal or increased levels of CFTR protein at the cell surface but a reduction in CFTR-mediated chloride transport. It has a prevalence of <0.1% globally. This mutation results in normal or elevated levels of CFTR protein at the cell surface but with reduced levels of CFTR function (average sweat chloride 45 mEq/L; 23% of patients with pancreatic insufficiency). Although asymptomatic at times, the D1152H mutation is associated with a broad clinical spectrum. Lung disease may be evident from infancy, and it is severe in some adults, although all have outlived the median life expectancy of CF.

2.3.2. Clinical study

Methods

Study Design

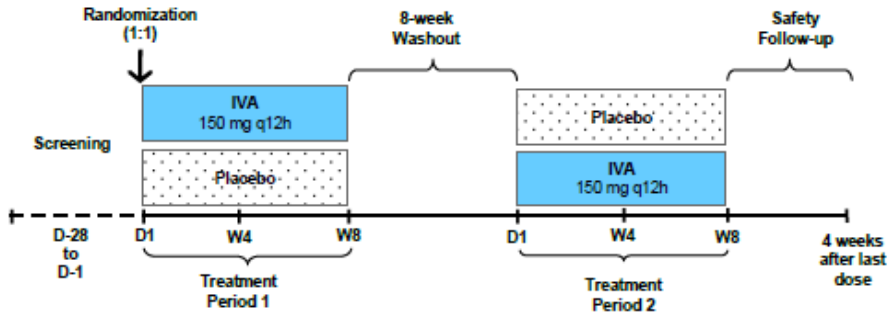
This is a randomized, double-blind, placebo-controlled, single-center, crossover study that includes two 8-week treatment periods separated by an 8-week washout period (Figure 9-1).

There will be 7 study visits, not including the Screening Visit. The total study duration for each subject will be approximately 32 weeks, including the Screening and the Follow-up periods.

- Sequence 1: ivacaftor (150 mg q12h) in Treatment Period 1; washout; placebo in Treatment Period 2

- Sequence 2: placebo in Treatment Period 1; washout; ivacaftor (150 mg q12h) in Treatment Period 2

Figure 9-1 VX16-770-127 Study Design



Objective(s)

Primary

To evaluate the efficacy of ivacaftor treatment in subjects with CF 6 years of age and older who have a 3849 + 10KB C→T or D1152H CFTR mutation.

Additional objectives

To explore the association between ivacaftor-induced CFTR function in *in vitro* organoid-based measurements and clinical response to ivacaftor in subjects with CF 6 years of age and older who have a 3849 + 10KB C→T or D1152H CFTR mutation.

Study endpoints

Primary

Change from baseline in lung clearance index2.5 (LCI2.5; calculated as lung volume turnovers required to reach 2.5% of the starting nitrogen [N2] concentration) through 8 weeks of treatment.

Additional endpoints

- Change from baseline in LCI5.0 (calculated as lung volume turnovers required to reach 5.0% of the starting N2 concentration) through 8 weeks of treatment

- Change from baseline in sweat chloride through 8 weeks of treatment.

- Change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at 8 weeks of treatment.

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) through 8 weeks of treatment.

- Organoid-based measurements of ivacaftor-induced CFTR function in vitro.

CHMP comments

Lung injury proceeds slowly and pulmonary function measured by spirometry can be apparently normal in young CF patients. That means that young patients with milder disease in whom lung function may not have begun to decline, FEV1 may not be sufficiently sensitive to detect a treatment effect. This is the reason why impaired lung clearance index (LCI), which measures the degree of small airway disease by assessing ventilation inhomogeneity, can be demonstrated in paediatric patients with normal spirometry. $LCI_{2.5}$ is more likely to reveal differences in ventilation homogeneity than $LCI_{5.0}$ as while $LCI_{2.5}$ measures the number of lung turnovers required to reduce the end tidal inert gas

concentration to 1/40th of its starting value, $LCI_{5.0}$ measures the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value.

While there is agreement on that the reduction in LCI reflects improvement in ventilation homogeneity, the experience with this test is still limited and it is somehow unknown the change from baseline that can be considered clinically relevant. The use of LCI as the primary endpoint is endorsed given that children older than 6 years were planned to be included in the trial. In addition, it can be applied to all age ranges. However, the results of this endpoint should be supported by evidence of clinical relevance from other endpoints.

$LCI_{5.0}$ was *evaluated as an additional endpoint. Other relevant endpoints were the change in ppFEV1, CFQ-R and sweat chloride and organoid-based measurements of ivacaftor-induced CFTR function in vitro. All are considered appropriate.*

Study population /Sample size

No formal sample size calculation was conducted. The planned sample size of approximately 50 subjects is based on the number of subjects expected to be available for participation.

Assuming an estimated standard deviation (SD) of the paired differences of 1.00 in LCI2.5, this available sample size of 50 subjects will produce a 2-sided 95% confidence interval (CI) of the mean treatment difference with precision (margin of error) of 0.28 points. Similarly, the margin of error using a 2-sided 80% CI will be 0.18 points.

CHMP comment

The sample size calculation has been focused on the precision to estimate the treatment difference through Week 8 in $LCI_{2.5}$ between IVA and placebo groups. 50 subjects were initially planned to participate in the study but instead, 38 have been randomized.

The MAH should explain numerically how this reduction of the planned sample size affects to the precision calculated and to the results presented.

Method of assessment efficacy and safety parameters

MBW (multiple-breath washout)

LCI2.5 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value, whereas LCI5.0 represents the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value.

Each MBW will be performed in multiple replicates for each visit, and the mean LCI value at each visit will be calculated by the sponsor or sponsor designee using all technically acceptable washout replicates provided by the central reader.

During the Screening Period, the MBW test may be performed pre- or post-bronchodilator. At all other visits, all MBW tests should be performed "pre-bronchodilator" and before the spirometry assessment. MBW testing must be performed before dosing, unless noted otherwise.

Pre-bronchodilator MBW testing is defined as MBW testing performed for subjects who have

- withheld their short-acting bronchodilator (e.g., albuterol) or anticholinergic (e.g., Atrovent) for more than 4 hours before the MBW testing; AND

- withheld their long-acting bronchodilator (e.g., salmeterol) more than 12 hours before the MBW testing; AND

- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the MBW testing.

In the event that a subject forgets to withhold bronchodilator(s), MBW testing should be performed according to the following:

- If the subject's Day 1 (in each treatment period) MBW test is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, post-bronchodilator MBW testing will be obtained for that visit only, and the visit will not be rescheduled.

- If at the subject's Day 1 (in each treatment period) MBW test, the subject forgets to withhold

his/her dose of bronchodilator, MBW testing should be performed post-bronchodilator and all subsequent MBW testing should be performed post-bronchodilator.

- Each MBW test will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

Subjects and their parent/caregiver should not be informed of their study-related LCI results during the study regardless if the subject has prematurely discontinued treatment.

Sweat Chloride Concentration

The sweat chloride test will be performed according to the standard operating procedure of the European Cystic Fibrosis Society - Clinical Trial Network (ECFS – CTN), using an approved Macroduct® (Wescor, Logan UT) collection device.Two gel patches that contain a chemical solution that stimulates sweat production of the skin by an electronic circuit will be placed on the subject's arm. Sweat samples will be sent to a central laboratory for testing. Individual sweat test results will not be disclosed to the study centers. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately.

CFQ-R Score

CFQ-R must be completed before the start of any assessments scheduled at that visit.

The version and format of CFQ-R will be based on age at Day 1, regardless of whether the subject changes age during the study. Parents/caregivers will complete the CFQ-Parent version on all visits.

The questionnaires provide information about demographics, general quality of life, school, work, or daily activities, and symptom difficulties (pertaining to CF). Copies of English and Hebrew versions of the CFQ-R used in this study will be provided in the Study Manual.

Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines the visits specified in Table 9-4 and according to the additional guidelines below.

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all other visits, all spirometry assessments should be performed pre-bronchodilator. Spirometry assessments must be performed before dosing, unless noted otherwise.

Pre-bronchodilator spirometry is defined as spirometry testing performed for subjects who have:

- withheld their short-acting β-agonist (e.g., albuterol) or anticholinergic (e.g., Atrovent) for more than 4 hours before the spirometry assessment; AND

- withheld their long-acting bronchodilator (e.g., salmeterol) for more than 12 hours before the spirometry assessment; AND

- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the spirometry assessment.

In the event that a subject forgets to withhold bronchodilators, spirometry should be performed

according to the following:

- If the subject's Day 1 (in each treatment period) spirometry is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.

- If at the subject's Day 1 (in each treatment period) spirometry the subject forgets to withold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements during the study should be performed post-bronchodilator.

- Each spirometry assessment will be recorded in the source documents as pre-bronchodilator

or post-bronchodilator.

The site will be provided spirometers to be used for all study assessments. Forced vital capacity (FVC), and FEV1 will be measured using a calibrated Masterlab pneumotachograph (Jaeger, Wűrzburg, Germany) or a comparable validated and calibrated device. Lung function equipment in the participating centers will be equally calibrated according to the ATS/ERS guidelines for lung function testing. Spirometry data will be transmitted to a centralized spirometry service for quality review.

The parameters listed below will be normalized using the GLI standards.

- FEV1 (L)

- Forced vital capacity (FVC) (L)

- FEV1/FVC (ratio)

- Forced expiratory flow (FEF25%-75%) (L/sec)

Subjects and their parent/caregiver should not be informed of their study-related spirometry results during the study regardless if the subject has prematurely discontinued treatment.

Weight, Height, and BMI

For subjects <21 years of age, weight, stature, and BMI, adjusted for sex and age will be summarized as weight-for-age, height-for-age, and BMI-for-age z-scores. Z-scores will be calculated using the Nutrition Examination Survey Growth Chart Equations.

Antibiotic Therapy for Sinopulmonary Signs/Symptoms

New or changed antibiotic therapy (IV, inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits as specified in Table 9-4.

- Change in sputum

- New or increased hemoptysis

- Increased cough

- Increased dyspnea

- Malaise, fatigue, or lethargy

- Temperature above 38°C (equivalent to approximately 100.4°F)

- Anorexia or weight loss

- Sinus pain or tenderness

- Change in sinus discharge

- Change in physical examination (PE) of the chest

- Decrease in pulmonary function by 10%

- Radiographic changes indicative of pulmonary infection

Pulmonary Exacerbations

For this study, pulmonary exacerbation is defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms. This definition is based on the definition of a pulmonary exacerbation used in previous clinical studies including IVA clinical studies.

It is recommended that study drug should not be interrupted during a pulmonary exacerbation unless, in the opinion of the investigator, it would be in the best interest of the subject.

The following information will be determined for protocol-defined pulmonary exacerbations:

- Number of pulmonary exacerbations

- Number of days with pulmonary exacerbations

- Time to first pulmonary exacerbation

- Number of pulmonary exacerbations requiring hospitalizations

- Number of days hospitalized for pulmonary exacerbations

- Time to first hospitalization for pulmonary exacerbation

- Number of pulmonary exacerbations requiring IV antibiotic therapy

- Number of days on IV antibiotic therapy for pulmonary exacerbations

- Time to first IV antibiotic therapy for pulmonary exacerbations

Hospitalization for CF

At visits specified in Table 9-4, subjects will be queried about planned and unplanned hospitalizations, defined as an admission including an overnight stay. The dates for hospitalizations and the reasons for hospitalizations will be documented.

If the hospitalization is unplanned, the procedures for safety reporting should also be followed. The following information will be determined:

- Number of planned hospitalizations for CF (i.e., prophylactic antibiotic therapy)

- Number of all unplanned hospitalizations

- Number of days of all unplanned hospitalizations

- Time to first unplanned hospitalization

Organoids

Biopsies of thirty-four CF patients were taken in Israel and shipped to Hubrecht Organoid Technology (HUB, The Netherlands) for organoid generation and evaluation of response to Ivacaftor (VX-770) by performing FIS (forskolin-induced swelling) assays. HUB has developed a technology which allows the

expansion of tissue, derived from cystic fibrosis patients. This primary tissue culture system, organoids, can yield patient specific samples in quantities that allow the screening of Vertex compounds. To assess the restoration of CFTR activity, a swelling assay is used to determine the effect of the compounds on specific CFTR mutations. In this study the organoids derived from the patients in the clinical trial are tested for their in vitro response to Ivacaftor.

Two biopsies failed to produce a viable organoid culture. All successfully established organoid cultures were frozen and stored at HUB. A dose response experiment consisting of 6 concentrations was performed for VX-770 in 5 different forskolin concentrations.

CHMP comments

The methods of assessment described are considered adequate.

Since cystic fibrosis is a systemic disease ivacaftor would be expected to impact not only on pulmonary function but also on other organs such as the gastrointestinal system. No data have been provided on this regard (e.g., change in BMI from baseline). However, given the short duration of the study is not likely that relevant changes in this endpoint can be seen.

Key inclusion criteria

Table 1 summarizes the principal inclusion criteria.

Table 1 Principal Inclusion Criteria and Enrollment of CF Subjects in Study 127

Enrollment Criteria	Study 127
Confirmed diagnosis of CF[5]	The subject had **both** of the following: • One or more characteristic phenotypic features, such as chronic cough and sputum production, persistent chest radiograph abnormalities, **or** airway obstruction manifested by wheezing and air trapping; **or** a history of CF in a sibling; **or** a positive newborn screening test result; • An increased sweat chloride concentration (≥60 mmol/L) by pilocarpine iontophoresis on 2 or more occasions; **or** identification of 2 CF causing mutations; **or** demonstration of abnormal nasal epithelial ion transport.
CFTR mutation	A *3849 + 10KB C→T* or *D1152H* mutation on at least 1 *CFTR* allele
Age and weight	6 years of age or older and weighing ≥25 kg on the date of the ICF
FEV_1	≥40% and ≤105% of predicted value at screening, based on the Global Lung Function Initiative (GLI)-2012 multi-ethnic all-age reference equations.[6]

Source: VX16-770-127 CSR/Section 9.3.1
CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 second; GLI: Global Lung Function Initiative; ICF: informed consent form

Key exclusion criteria

Key exclusion criteria included the following: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H CFTR mutation

- History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. For example:

- A history of cirrhosis with portal hypertension.

- An acute upper or lower respiratory infection, pulmonary exacerbation (PEx), or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (the first dose of study drug).

CHMP comments

The inclusion and exclusion criteria are acceptable for the purpose of the study.

Prior and Concomitant Medications

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered from 30 days before the Screening Period through the Safety Follow-up Visit will be recorded in each subject's source documents and electronic case report form (eCRF). For subjects who are screened but are not enrolled in the study, details of prior medications will only be documented in the subjects' source documents.

Information about bronchodilator use during the study will be collected and documented in the

subject's source documents and eCRF.

CHMP comments

Definition of prior and concomitant medication is acceptable.

Maintenance of Stable Medication Regimen for CF

It is recommended that subjects remain on stable CF medication regimens from 4 weeks before Day 1 through the end of the study. A stable medication regimen is defined as a medication regimen that the subject has been following for at least 4 weeks before Day 1.

Specific requirements apply to certain CF medications:

- At the time of study entry, subjects who are on a stable regimen of a single inhaled antibiotic that is continuously administered should remain on this antibiotic through the Safety Follow-up Visit.

- At the time of study entry, subjects who are on a stable regimen of a single inhaled cycling antibiotic (e.g., Tobramycin Inhalation Solution [TOBI®] regimen), should remain on this antibiotic through the Safety Follow-up Visit. Inhaled cycling antibiotics should be administered in 28-day-on/28-day-off cycles. Study visits on Day 1 and Week 8 during Treatment Periods 1 and 2 should be timed to occur at the end of an off-cycle, but no fewer than 14 days after the last dose of inhaled antibiotics in the previous on-cycle.

- At the time of study entry, subjects who are on an alternating regimen of inhaled cycling antibiotics that comprise continuous administration of antibiotics (e.g., TOBI administration alternating with Cayston®) should remain on these antibiotics according to their alternating regimens through the Safety Follow-up Visit.

Administration

Study drug tablets will be administered orally. During Treatment Period 1 and Treatment Period 2 subjects will take 1 tablet (ivacaftor [150 mg] or matching placebo) twice per day. Study drug should be administered within 30 minutes of consuming fat-containing food such as a standard CF high-fat, high-calorie meal or snack according to the following guidelines:

- All doses of study drug (morning and evening, as applicable) should be administered at approximately q12 h (± 2 hours) on each dosing occasion (e.g., if the morning doses of study drug are administered at 08:00 hours on Day 1, all subsequent morning doses should be administered between 06:00 hours and 10:00 hours).

- At study visits during the treatment periods, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.

- If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used for administering either the morning or evening dose:

    o If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of study drug and the morning dose will be administered in the clinic.

    o If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.

- For the visit at the end of each treatment period, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.

Dose Modification for Toxicity

If any unacceptable toxicity arises, individual subjects will discontinue dosing.

Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. Study drug treatment will be withdrawn for any female subject who has a confirmed pregnancy and for any male subject whose female partner has a confirmed pregnancy. A subject may be withdrawn from study drug treatment after a discussion between the investigator and the medical monitor for any of the following reasons:

- The subject develops a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.

- The subject has an increase in transaminases for which withdrawal of study drug is recommended

- The subject develops a cataract.

If a subject has been withdrawn from study drug treatment, the subject will continue to be followed, provided the subject has not withdrawn consent.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws consent for the study, no further evaluations will be performed and no additional data will be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

Blinding and Unblinding

This will be a double-blind study. Subjects and all site personnel, including the investigator, site monitor, and study team, will remain blinded to treatment assignments until database lock. The Vertex study team will remain blinded to treatment assignments until all subjects have completed the study. Exceptions are made for the following personnel:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency

- Any site personnel for whom this information is important to ensure the safety of the subject and the fetus in the event of a pregnancy

- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations

- Unblinded statistician who will prepare the final (production) randomization list (this statistician is not part of the study team)

- Vertex IXRS Management for IXRS oversight and system administration

- Vertex Clinical Supply Chain

- The bioanalytical laboratory/vendor personnel managed by Vertex Bioanalysis.

Vertex Quality Assurance GCP personnel and all other Vertex Bioanalysis laboratory personnel will be blinded to the treatment assignment.

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding.

If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor.

Timing of assessments

The timing of assessment is shown in table below.

Table 9-4 Study VX16-770-127: Treatment Period and Follow-up Visit Assessments

Event/Assessment	Treatment Period 1			Washout Period	Treatment Period 2			Early Termination of Treatment (ETT)	Safety Follow-up 4 weeks (± 7 days) after last dose of study drug[a]
	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)	8 weeks (± 4 days)	Day 1	Week 4 (± 4 days)	Week 8 (± 4 days)		
Review of inclusion /exclusion criteria	X								
Randomization	X								
CFQ-R[b]	X		X		X		X		
Meal(s) or snack(s) at site[c]	X	X	X		X	X	X		
Vital signs[d]	X	X	X		X	X	X	X	X
Weight[e]	X	X	X		X	X	X	X	X
Height[e]	X		X		X		X		
Physical examination	X		X		X		X	X	X
MBW[f]	X	X	X		X	X	X		
Spirometry[f]	X	X	X		X	X	X		
Sweat chloride	X	X	X		X	X	X		
Other events related to outcome[g]	X	X	X		X	X	X		
Pregnancy test (female subjects of childbearing potential)[h]	X	X	X		X	X	X	X	X
LFTs[i]	X		X		X		X	X	X
Amylase and lipase	X		X		X		X	X	X
OE[j]							X	X	
IVA or placebo dosing	X	X	X		X	X	X		
Concomitant treatments and procedures	Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit								
Adverse events	Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit								

ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ETT: early termination of treatment; GGT: gamma-glutamyl transferase; ICF: informed consent form; LFT: liver function test; OE: ophthalmologic examination; MBW: multiple breath washout; IVA: ivacaftor

[a] If the ETT Visit occurred ≥3 weeks after the last dose of study drug, the Follow-up Visit was not required.
[b] The CFQ-R assessment must have been completed before the start of any other assessments scheduled at that visit.
[c] Fat-containing food such as a standard CF high-fat, high-calorie meal or snack was provided to subjects at the site after all pre-dose assessments have occurred.
[d] Vital signs (blood pressure, pulse rate, respiration rate, and body temperature) were collected after the subject had been at rest (supine) for 5 minutes. Blood pressure was measured by sphygmomanometer. Vital sign assessments were performed before blood draws.
[e] Weight and height were measured with shoes off. Height was measured at Day 1 and Week 8 only for subjects <21 years of age at the Screening Visit.
[f] MBW and spirometry were performed pre-bronchodilator and before the spirometry assessment, and must have been performed before dosing.
[g] Other events related to outcome included assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations for CF (Appendix 16.1.1/Protocol Version 1.0/Section 11.4.6).
[h] A urine β-hCG test will be performed at all visits in Treatment Periods 1 and 2 and will be performed before the first dose of study drug on Day 1 of Treatment Periods 1 and 2. A urine β-hCG test will be performed at the ETT Visit (as applicable). A serum pregnancy test will be performed at the Safety Follow-up Visit.
[i] ALT, AST, GGT, alkaline phosphatase, and bilirubin
[j] OE is required for subjects who were under 18 years of age at the Screening Visit. OE will be performed either at the Week 8 Visit of Treatment Period 2 or at the ETT Visit. This examination is not required if the subject received study drug for a total of less than 4 weeks.

Safety

Elevation of LFT Parameters

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN must be followed closely, including repeat confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. In addition, if ALT or AST are >5 × ULN, repeat follow-up levels must be obtained within 7 ± 2 days and followed up 7 days later. If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory must be reported immediately to the medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

LFT Elevations Leading to Study Drug Interruption.

Study drug administration must be interrupted immediately, and the medical monitor must be notified if any of the following criteria is met:

- ALT or AST >5 × ULN, or

- ALT or AST >3 × ULN in association with elevation of bilirubin >2 × ULN and/or clinical jaundice.

Repeat testing should be performed within 48 to 72 hours to confirm the initial elevation. A thorough investigation of potential causes should be conducted, and the subject should be followed closely for clinical progression. If no convincing alternative etiology for the elevated transaminases is identified, regardless of whether ALT or AST levels have improved, the subject must be discontinued from the study in consultation with the medical monitor.

Subjects in whom treatment is discontinued for elevated transaminases should have their transaminases monitored closely until levels normalize or return to baseline. If an alternative cause of transaminase elevation has been identified, study drug may be resumed once transaminases return to ≤2 × ULN. Approval of the medical monitor is required before resumption of study drug. Upon resumption of study drug, transaminases should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation occurs within 4 weeks of rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed etiology.

Physical Examinations and Vital Signs

A physical examination (PE) of all body systems and vital signs assessment will be performed at screening and select study visits (Table 9-4). At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

A PE includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat; respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

Vital signs include blood pressure (systolic and diastolic), body temperature, pulse rate, and respiration rate. These will be assessed following at least a 5-minute rest in the supine position.

Ophthalmologic Examination

Subjects who are under 18 years of age at the Screening Visit will undergo an OE at the time points in the protocol and Table 9-4. The OE will include:

- measurement of best corrected distance visual acuity of each eye

- pharmacologically dilated examination of the lens with a slit lamp

These examinations must be conducted by a licensed ophthalmologist or optometrist. If there is documentation of an OE that met protocol criteria and was conducted within 3 months before the

Screening Visit, the subject is not required to have another OE during Screening. If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist or optometrist, the subject (and the subject's parent or guardian if the subject is a minor) will be notified.

Additional OEs may be conducted at the discretion of the investigator. The Vertex medical monitor or designee should be notified of any additional OEs.

In addition, at Screening, the following history will be obtained for all subjects:

- history of steroid use

- history of trauma to the eye

- any family history of glaucoma, congenital cataracts, or cataracts arising later in life.

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry at Screening	Hematology at Screening	Liver Function Tests[a]
Glucose	Hemoglobin	Bilirubin, direct bilirubin
Blood urea nitrogen	Erythrocytes:	Aspartate aminotransferase
Creatinine	Mean corpuscular hemoglobin	Alanine aminotransferase
Sodium	Mean corpuscular hemoglobin concentration	Gamma glutamyl transferase
Potassium	Mean corpuscular volume	Alkaline phosphatase
Calcium	Platelets	
Chloride	Reticulocytes (absolute)	
Magnesium	Leukocytes	
Bicarbonate	Differential (absolute and percent):	
Phosphate	Eosinophils	
Bilirubin, direct bilirubin	Basophils	
Alkaline phosphatase	Neutrophils	
Aspartate aminotransferase	Lymphocytes	
Alanine aminotransferase	Monocytes	
Amylase[a]		
Lactate dehydrogenase		
Lipase[a]		
Gamma glutamyl transferase		
Protein		
Albumin		
Creatine kinase		

[a] Amylase, lipase, and LFTs performed at screening and at other Visits as indicated in Table 3-2.

CHMP comments

Safety endpoints are deemed appropriate as they cover the most relevant AEs identified with Kalydeco.

Statistical Methods

Sample size calculation

No formal sample size calculation was conducted. The planned sample size of approximately 50 subjects is based on the number of subjects expected to be available for participation. Assuming an estimated standard deviation (SD) of the paired differences of 1.00 in LCI2.5, this available sample size of 50 subjects will produce a 2-sided 95% confidence interval (CI) of the mean treatment difference with precision (margin of error) of 0.28 points. Similarly, the margin of error using a 2-sided 80% CI will be 0.18 points.

CHMP comments

The sample size calculation has been focused on the precision to estimate the treatment difference through Week 8 in LCI2.5 between IVA and placebo groups. 50 subjects were initially planned to participate in the study but instead, 38 have been randomized.

The Applicant should explain numerically how this reduction of the planned sample size affects to the precision calculated and to the results presented.

Analysis Sets

The Full Analysis Set (FAS) is defined as all randomized subjects who have received at least 1 dose of study drug.

The Safety Set is defined as all enrolled subjects who received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the

treatment they received and not according to their randomized treatment group.

Statistical Analyses

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, standard error, median, minimum value, and maximum value.

Categorical variables will be summarized using counts and percentages.

Baseline: Study baseline is defined as the most recent nonmissing measurement collected before

the first administration of study drug in Treatment Period 1. Period baseline is defined as the most recent nonmissing measurement collected before the first administration of study drug in each Treatment Period. For Treatment Period 1, the period baseline will be the study baseline; for Treatment Period 2, the period baseline will be from an assessment measured after the Washout Period and before the first administration of study drug in Period 2.

For all efficacy analyses, the statistical inference will be based on change from study baseline. However, efficacy analyses based on change from period baseline will also be presented. Similarly, summary tables, as applicable, will be presented based on both baselines. All subject data, including those derived, will be presented in the subject data listings; listings will display all subjects who were randomized, regardless of whether or not they received study drug.

Efficacy analysis

Change from Baseline in LCI

A Bayesian approach will be used to estimate the effect of ivacaftor versus placebo on change from

study baseline in LCI2.5. A non-informative prior distribution (normal distribution with mean 0 and variance = 10^6) on the treatment difference will be assumed. The posterior distribution of the treatment difference will be obtained using the Markov Chain Monte Carlo (MCMC) method.

The mean of the posterior distribution will be calculated and the 80% credible interval for the treatment difference will be provided. Using this Bayesian method, the posterior probability that

the treatment difference for LCI2.5 is less than zero will be calculated. The study will be considered successful if this probability exceeds 80%.

Supportive analyses of absolute change from study baseline in LCI2.5 through Week 8 of each double-blind treatment period based on a mixed-effects model for repeated measures (MMRM) using the FAS will be performed.

The model will include the absolute change from the study baseline in each treatment period as the dependent variable; sequence, treatment, treatment period, and visit within treatment period as fixed effects; LCI2.5 at study baseline as covariate if deemed necessary; and subject nested within sequence as the random effect. An unstructured covariance matrix will be used for the repeated measurements of the same subject within each treatment period. If there is a convergence problem for the unstructured covariance matrix, an appropriate covariance matrix structure, such as compound symmetry, will be assumed in the primary analysis. The estimated mean treatment difference overall, and a 80% confidence interval will be provided.

Carry-over effect will be assessed by the sequence effect in the model, as well as by comparing baseline for each treatment period. If there is a clinically or statistically significant unequal carry-over effect, then the data from the first period may be used for the analysis.

As a sensitivity analysis, the analysis will be repeated using change from period baseline instead of change from study baseline. Summary, plots, and individual listings of efficacy data will be generated. A more detailed description of the planned statistical analysis of efficacy endpoints will be presented in the SAP.

Change from Baseline in LCI5.0, Sweat Chloride, and ppFEV1

Analysis for change from study baseline in LCI5.0, sweat chloride (mmol/L), and ppFEV1, will be similar to the analysis of change from baseline in LCI2.5.

CFQ-R Score

The raw scores in CFQ-R will be summarized into different domains of health (12 domains for subjects 14 years of age and older; 8 for subjects 6 to 13 years of age; and 11 for parents/caregivers). The primary analytical focus will be the respiratory domain using a pooling of all self-response questionnaire versions (e.g., Adult/Adolescent and Child versions).

Respiratory domain will be analyzed using a mixed effects model with baseline measurement as covariate if deemed necessary.

Subgroup Analysis of Interest

Subgroup analyses of LCI among subjects with a pre-determined minimum ppFEV1 at baseline (e.g., at least 60 percent predicted) may be performed using MMRM in a similar manner as described for primary endpoint LCI2.5.

Similar analyses of ppFEV1 among subgroup of subjects with a pre-determined maximum value at baseline (e.g., ≤90 percent predicted) may be performed.

These analyses will be described in more detail in the SAP prior to the database lock.

Events Related to Outcome

Pulmonary exacerbations, hospitalizations, and related outcomes will be summarized for each treatment group as appropriate.

Organoid assessment

In total, five forskolin concentrations and six VX-770 concentrations were tested, for a total of thirty experimental conditions for the assay.

Two measures of organoid swelling were used for analysis: the AUC value and the maximum value of the organoid swelling over 90 minutes. Values were obtained in triplicate at each of two biological replicates per experimental condition.

Background-corrected values were generated for the average of the 2 biological replicates from each triplicate measurement for both organoid swelling measures. These values were used to explore the association between organoid swelling measures and clinical measures.

Analysis of AUC value of In Vitro Organoid Swelling

A descriptive summary of the background corrected value of AUC was provided for each experimental condition corresponding to FRSK and VX-770 concentrations, by CFTR genotype for Mutation 1 (3849 + 10KB C→T and D1152H).

Dose-response curves of the mean background corrected AUC versus the FRSK concentration were provided for each VX-770 dose, by the CFTR genotype for Mutation 1. Further, for each CFTR genotype for Mutation 1, a Pearson correlation analysis was performed of background corrected AUC versus placebo-corrected change from study baseline at Week 8 on IVA for each of the clinical endpoints (LCI2.5, ppFEV1, and sweat chloride) at each experimental condition corresponding to different FRSK and VX-770 concentrations.

Analysis of Maximum Value of In Vitro Organoid Swelling

The analysis was similar to that for the AUC value of the organoid swelling.

Safety

The overall safety profile of ivacaftor will be assessed in terms of:

- Incidence of treatment-emergent adverse events (TEAEs)

- Clinical laboratory values (e.g., LFTs)

- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) and PEs

- OEs (for subjects less than 18 years of age)

Safety analyses will be based on the Safety Set. All safety data will be presented in subject data listings.

Adverse Events

AEs will be coded according to MedDRA. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA system organ class and preferred term. AEs will be classified as pre-treatment or treatment-emergent.

Pre-treatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing.

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the Safety Follow-up Visit.

Only TEAEs will be summarized in tables. Some rules that will apply to the summarization of AEs are (1) a subject with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary;

and (3) only the worst relationship level will be presented in the relationship summary.

AEs leading to death, SAEs, dose interruption, and permanent discontinuation will be listed separately. All AEs through the Safety Follow-up Visit, including pre-treatment AEs, will be listed in a subject data listing.

Clinical Laboratory Assessments

All statistical summaries of laboratory values will be performed using SI units. LFT results will be summarized by treatment group at each scheduled time point. Changes from baseline will also be summarized. Maximum shift changes from baseline based on the LFT normal ranges will be tabulated by treatment. A subject data listing of abnormal LFT values from scheduled and unscheduled time points will be provided. Results for hematology and for chemistry assessments other than LFTs will be listed. Clinically significant abnormal laboratory findings will be reported as AEs.

Vital Signs

Systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute), and body temperature (degrees C) will be summarized by treatment.

Changes from baseline will also be summarized. Clinically significant abnormal findings will be reported as AEs.

Physical Examination

PE results performed as part of the Screening Period assessment will be presented in subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

Ophthalmological Examinations

Ophthalmological examination will be done for subjects who are under 18 years of age at the Screening Visit and then either at the Week 24 Visit or at the ETT Visit. This examination is not required if the subject received study drug for a total of less than 4 weeks.

Ophthalmologic examination findings will be presented as a data listing. Summary tables will be provided if deemed necessary and as appropriate.

Results

Recruitment/ Number analysed

Thirty-eight subjects were randomized, dosed, and completed the study. One subject prematurely discontinued study drug treatment due to pregnancy.

Table below shows the subject disposition in the study.

Table 10-1 Subject Disposition, All Subjects Set

Disposition Category	Treatment Sequence 1[a] n (%)	Treatment Sequence 2[b] n (%)	Total n (%)
All subjects (randomized or dosed)	19	19	38
Randomized	19	19	38
Safety Set	19	19	38
Full Analysis Set	19	19	38
Treatment Period 1			
Completed study drug treatment	19 (100.0)	19 (100.0)	38 (100.0)
Treatment Period 2			
Completed study drug treatment	19 (100.0)	18 (94.7)	37 (97.4)
Discontinued study drug treatment	0	1 (5.3)	1 (2.6)
Reason for discontinuation			
Pregnancy (self)	0	1 (5.3)	1 (2.6)
Completed study	19 (100.0)	19 (100.0)	38 (100.0)

Source: Table 14.1.1

Notes: Percentages were calculated relative to the number of Subjects in the Full Analysis Set. Full Analysis Set: All subjects who were randomized or received at least 1 dose of study drug; Safety Set: All subjects who received at least 1 dose of the study drug.

[a] Treatment Sequence 1: IVA in Treatment Period 1→Washout→placebo in Treatment Period 2

[b] Treatment Sequence 2: placebo in Treatment Period 1→Washout→IVA in Treatment Period 2

Tables below are showing the demographic and the baseline characteristics.

Table 10-2 Subject Demographics, FAS

Variable	Treatment Sequence 1[a] N = 19	Treatment Sequence 2[b] N = 19	Total N = 38
Genotype for Mutation 1, n (%)			
3849 + 10KB C→T	11 (57.9)	11 (57.9)	22 (57.9)
D1152H	8 (42.1)	8 (42.1)	16 (42.1)
Sex, n (%)			
Male	9 (47.4)	9 (47.4)	18 (47.4)
Female	10 (52.6)	10 (52.6)	20 (52.6)
Childbearing potential, n (%)			
Yes[c]	6 (60.0)	8 (80.0)	14 (70.0)
No[c]	4 (40.0)	2 (20.0)	6 (30.0)
Age at baseline (years)			
n	19	19	38
Mean (SD)	32.6 (15.3)	32.1 (15.6)	32.3 (15.2)
SE	3.5	3.6	2.5
Median	33.0	33.0	33.0
Min, Max	8, 64	7, 58	7, 64
Ethnicity, n (%)			
Not Hispanic or Latino	19 (100.0)	19 (100.0)	38 (100.0)
Race, n (%)			
White	19 (100.0)	19 (100.0)	38 (100.0)

Source: Table 14.1.2

FAS: Full Analysis Set; max: maximum value; min: minimum value; N: total sample size; n: size of subsample; SD: standard deviation; SE: standard error

Note: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1.

[a] Treatment Sequence 1: IVA in Treatment Period 1→Washout→placebo in Treatment Period 2

[b] Treatment Sequence 2: placebo in Treatment Period 1→Washout→IVA in Treatment Period 2

[c] Percentages under child-bearing potential were calculated relative to the number of female subjects.

Table 10-3 Baseline Characteristics, FAS

Characteristics	Treatment Sequence 1[a] N = 19 n (%)	Treatment Sequence 2[b] N = 19 n (%)	Total N = 38 n (%)
$ppFEV_1$ at screening			
<60	4 (21.1)	4 (21.1)	8 (21.1)
≥60	15 (78.9)	15 (78.9)	30 (78.9)
Age group at screening (years)			
<12	2 (10.5)	2 (10.5)	4 (10.5)
≥12	17 (89.5)	17 (89.5)	34 (89.5)
$ppFEV_1$ category			
<40	0	0	0
≥40 and <70	9 (47.4)	9 (47.4)	18 (47.4)
≥70 and ≤90	5 (26.3)	6 (31.6)	11 (28.9)
>90	5 (26.3)	4 (21.1)	9 (23.7)
$ppFEV_1$			
n	19	19	38
Mean (SD)	74.8 (17.6)	73.1 (16.5)	74.0 (16.9)
SE	4.0	3.8	2.7
Median	79.6	70.8	71.7
Min, Max	44.6, 102.0	43.5, 96.1	43.5, 102.0
FEV_1			
n	19	19	38
Mean (SD)	2.46 (0.85)	2.44 (0.71)	2.45 (0.77)
SE	0.19	0.16	0.12
Median	2.56	2.32	2.40
Min, Max	1.22, 3.73	1.41, 4.26	1.22, 4.26
$LCI_{2.5}$			
n	19	19	38
Mean (SD)	12.74 (4.04)	13.19 (5.45)	12.96 (4.74)
SE	0.93	1.25	0.77
Median	12.19	12.03	12.11
Min, Max	6.61, 21.36	6.75, 25.47	6.61, 25.47
$LCI_{5.0}$			
n	19	19	38
Mean (SD)	7.76 (2.03)	7.71 (2.32)	7.73 (2.15)
SE	0.46	0.53	0.35
Median	6.81	7.10	7.07
Min, Max	4.88, 11.41	4.90, 13.24	4.88, 13.24
Sweat Chloride (mmol/L)			
n	19	19	38
Mean (SD)	50.6 (23.9)	47.6 (24.7)	49.1 (24.0)
SE	5.5	5.7	3.9
Median	41.5	52.0	43.5
Min, Max	18.0, 96.5	12.0, 108.0	12.0, 108.0
CFQ-R respiratory			

CHMP comments

The demographic characteristics are presented for the FAS population that comprises 38 patients. These baseline characteristics were very similar for the patients in both sequences. Subjects were equally distributed between both mutations in both sequences and slightly more patients (57.9%) had 3849+10kbC->T mutation (42.1% for D1152H).

For the study of organoids (see page 44) the MAH has provided information about the mutation in the second allele in 34 out of the 38 patients included in the study.

- Most patients with the 3849+10kbC->T mutation (n=19) had the W1282X mutation (n=12) or the F508del (n=5) in the second allele. According to the CFTR2 database these variant combinations causes CF. Patients with CF who have these variants are likely to be pancreatic sufficient.

- Most patients with the D1152H mutation (n=15) had also the W1282X mutation (n=5) or the F508del (n=4). According to the CFTR2 database, these variant combinations have varying consequences so some patients have CF and some do not. Patients with CF who have this variant are likely to be pancreatic sufficient.

Baseline ppFEV1 was ≥40 and < 70% in around 50% of patients in both sequences (47.4%); no patients had ppFEV1 <40% at baseline. Twenty six percent (26.3%) and 31.6% had ppFEV ≥ 70 and ≤90 and 26.3% and 21.1% ppFEV1 >90% in sequences 1 and 2, respectively. $LCI_{2.5}$ at baseline was around 13 in both sequences with minimum values in some patients of 6.61 and 6.75 and maximum values of 21.36 and 25.47, respectively (normal value <7.5). This would be reflective of uneven ventilation and small airways disease in most of patients. In general, the patients seem to have a lung function moderately affected.

Sweat chloride was 41.5 and 52.0 mmol/L for patients on sequence 1 and 2 and minimum values of 18 and 12 mmol/L, respectively. Such low values, however, are considered not likely indicative of cystic fibrosis. It would have been desirable that a sweat chloride at baseline equal or above 60 mmol/l had been requested for all patients. The MAH should provide individual data of patients with sweat chloride values under 60 mmol/L and the corresponding mutation.

Only 2 subjects were younger than 12 years of age in each sequence of treatment and the rest of patients are reported as older than 12 years. No information is provided about the exact number of paediatric patients and their baseline characteristics. However, for the purpose of this application (submission of data under Art 46 of the "Paediatric Regulation") it would be of interest to have efficacy and safety data in this population if the paediatric population (patients younger than 18 years of age) were a substantial proportion of the whole population (i.e., 50% or more).

Medical history

The most common medical history conditions (incidence ≥15% of subjects by PT in the FAS) are summarized in Table below.

Table 10-4 Medical History With an Incidence of At Least 15% of Subjects in Any Treatment Sequence FAS

System Organ Class Preferred Term	Treatment Sequence 1[a] N = 19 n (%)	Treatment Sequence 2[b] N = 19 n (%)	Total N = 38 n (%)
Subjects with any medical history	19 (100.0)	19 (100.0)	38 (100.0)
Congenital, familial and genetic disorders	19 (100.0)	19 (100.0)	38 (100.0)
Bronchiectasis	8 (42.1)	3 (15.8)	11 (28.9)
Asthma	4 (21.1)	5 (26.3)	9 (23.7)
Nasal polyps	4 (21.1)	3 (15.8)	7 (18.4)
Haemoptysis	2 (10.5)	3 (15.8)	5 (13.2)
Gastrointestinal disorders	12 (63.2)	8 (42.1)	20 (52.6)
Pancreatitis	4 (21.1)	4 (21.1)	8 (21.1)
Gastrooesophageal reflux disease	5 (26.3)	2 (10.5)	7 (18.4)
Pancreatic failure	3 (15.8)	1 (5.3)	4 (10.5)
Infections and infestations	12 (63.2)	8 (42.1)	20 (52.6)
Bacterial disease carrier	4 (21.1)	4 (21.1)	8 (21.1)
Bronchopulmonary aspergillosis allergic	2 (10.5)	3 (15.8)	5 (13.2)
Chronic sinusitis	5 (26.3)	0	5 (13.2)
Surgical and medical procedures	10 (52.6)	5 (26.3)	15 (39.5)
Sinus operation	3 (15.8)	3 (15.8)	6 (15.8)
Musculoskeletal and connective tissue disorders	5 (26.3)	4 (21.1)	9 (23.7)
Clubbing	1 (5.3)	4 (21.1)	5 (13.2)
Osteopenia	3 (15.8)	1 (5.3)	4 (10.5)
Immune system disorders	5 (26.3)	3 (15.8)	8 (21.1)
Drug hypersensitivity	5 (26.3)	2 (10.5)	7 (18.4)

Source: Table 14.1.4
FAS: full analysis set; N: total sample size; n: size of subsample

CHMP comments

Patients with 3849 + 10KB C→T or D1152H-CFTR mutations are expected to be pancreatic sufficient. However, some cases of pancreatitis and pancreatic failure for some patients in both sequences (3 in sequence 1 and 1 in sequence 2) that could be indicative of pancreatic insufficiency.

Concomitant Medications

The majority (94.7%) of subjects used medication prior to receiving the first dose of study drug. Medication regimens were generally similar before study (prior medication) and during the treatment period (concomitant medication), and while receiving either of the study drugs.

Table 10-5 summarizes concomitant medications taken by at least 15% of subjects while receiving placebo or IVA. The most common (≥40% incidence overall) concomitant medications were indicated for management of CF complications and included dornase alpha, sodium chloride, and azithromycin.

Table 10-5 Concomitant Medications Received by At Least 15% of Subjects in Any Treatment Sequence, FAS

Preferred Name	Placebo N = 38 n (%)	IVA N = 38 n (%)
Subjects with Any Concomitant Medication	38 (100.0)	37 (97.4)
Dornase alpha	29 (76.3)	28 (73.7)
Sodium chloride	28 (73.7)	28 (73.7)
Azithromycin	16 (42.1)	16 (42.1)
Ciprofloxacin	14 (36.8)	14 (36.8)
Vitamin D	12 (31.6)	12 (31.6)
Salbutamol	11 (28.9)	11 (28.9)
Tobramycin	10 (26.3)	9 (23.7)
Budesonide with formoterol fumarate	8 (21.1)	8 (21.1)
Colistin	7 (18.4)	7 (18.4)
Omeprazole	7 (18.4)	7 (18.4)
Bactrim	8 (21.1)	6 (15.8)
Colistimethate sodium	5 (13.2)	6 (15.8)
Seretide	6 (15.8)	6 (15.8)

Source: Table 14.1.6
FAS: full analysis set; IVA: ivacaftor; n: size of subsample; N: total sample size; WHO-DDE: World Health Organization Drug Dictionary Enhanced
Notes: Medications were coded using WHO-DDE, version March 2017, format B2. Preferred Names are sorted in descending order of frequency based on IVA column. A subject with multiple medications within a category was counted only once within that category.

CHMP comments

Virtually all patients received concomitant medications. Both treatment sequences behaved very similar although more patients in the sequence 1 had bronchiectasis (73.7% versus 42.1%), chronic sinusitis (26.3% versus 0) and osteopenia (15.8 versus 5.3%; respectively). No differences are observed in terms of concomitant treatment as except for Bactrim that was given to more patients in sequence 1 (21.1% versus 15.8%) in the rest of drugs the percentages are virtually identical.

Important Protocol Deviations

An IPD was defined as any protocol deviation that had the potential to significantly impact the completeness, accuracy, or reliability of the study data or that may have significantly affected a subject's rights, safety, or well-being.

Five IPDs were reported in 5 subjects (1 subject in Treatment Sequence 1 and 4 subjects in Treatment Sequence 2). The IPDs were related to changes in pulmonary disease within 4 weeks of Day 1 of a treatment period, treatment compliance <80%, and missed safety assessments. The IPDs are briefly described below.

IPDs involving acute upper respiratory infection, PEx, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before the Treatment Period 2, Day 1 Visit.

It is unlikely that these IPDs impacted the ability to interpret the overall study results given their timing relative to the Treatment Period 2 start date and the number of subjects affected.

• One subject had an IPD of PEx during the washout period. The PEx lasted 15 days and the subject received antibiotic treatment during that time. The subject had the Treatment Period 2 Day 1 visit less than 4 weeks after the end date of the PEx and antibiotic treatment.

• One subject had an IPD of common cold which ended with no antibiotic treatment. The cold involved an acute upper or lower respiratory tract infection. The subject had the Treatment Period 2 Day 1 visit less than 4 weeks after the cold ended. According to the MAH, it is unlikely that this IPD impacted the ability to interpret the overall study results, given it involved only 1 subject.

• One subject had an IPD of less than 80% treatment compliance during both study periods. The subject was 76.7% compliant during Treatment Period 1 and 75% compliant during Treatment Period 2.

• One subject had an IPD of serum pregnancy test not performed during screening. The site collected a serum sample for this pregnancy test, but the sample was not appropriately identified, hence the test could not be completed. The subject's subsequent pregnancy tests were all negative.

• One subject had an IPD of urine pregnancy test not performed at the Treatment Period 2, Week 4 Visit. Reportedly, the subject could not produce urine for the test. The subject later had a confirmed pregnancy and therefore discontinued study drug treatment.

No safety issues were identified for these subjects.

CHMP comment

The protocol deviations are not likely to have affected the study outcome.

EFFICACY RESULTS

Primary analysis

The primary efficacy endpoint was the absolute change from baseline in LCI2.5 through 8 weeks of treatment. The Bayesian analysis of the primary endpoint (through Week 8) is presented in table below.

Table 11-1 Bayesian Analysis: Posterior Mean of Change From Baseline in $LCI_{2.5}$ Through Week 8, FAS

Change from Baseline Through Week 8	IVA-Placebo
n	38
Posterior Mean (SD)	-0.68 (0.23)
Median	-0.68
25^{th} percentile	-0.83
75^{th} percentile	-0.53
Posterior probability that average treatment difference through Week 8 (IVA-Placebo) < 0	0.9976

Source: Table 14.2.1.2

FAS: full analysis set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; n: size of subsample; SD: standard deviation

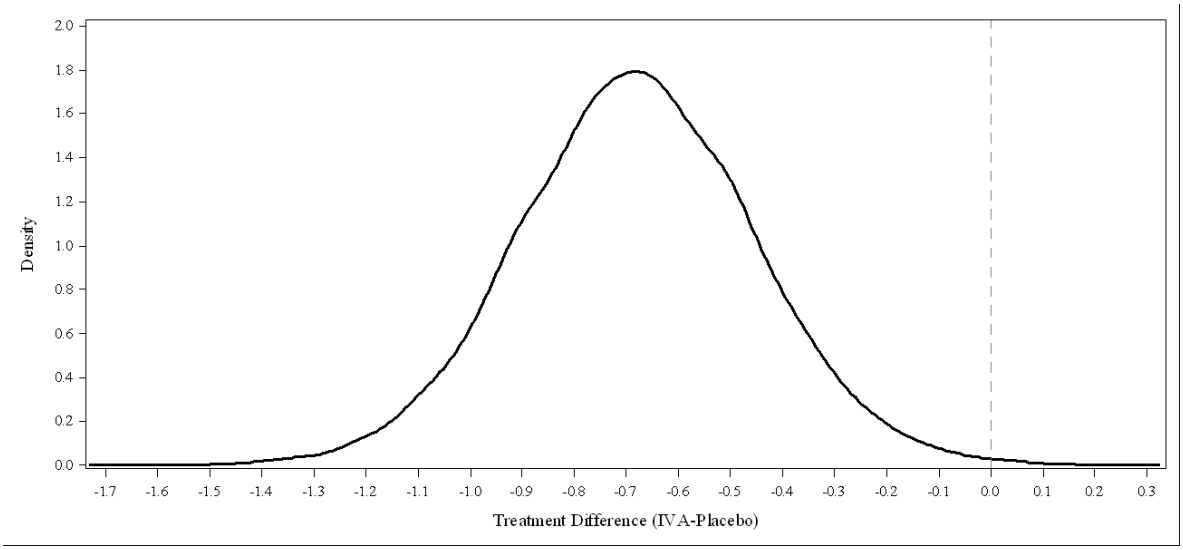
Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug. Repeated Measures Model: sequence by period by visit were cell effects, with baseline $LCI_{2.5}$ as a covariate; Covariance Structure=UN@CS; non-informative prior for cell effects and covariate effect; flat prior for variance-covariance parameters.

The Bayesian posterior probability of a <0 average treatment difference through Week 8 between

the IVA and placebo groups in the change from baseline in LCI2.5 was >99% (posterior mean: -0.68; 25th percentile: -0.83, 75th percentile: -0.53). A negative change in LCI2.5 is indicative of

improvement with IVA treatment compared to placebo. The posterior distribution of average treatment difference is shown in Figure 11-1.

Figure 11-1 Posterior Distribution of Average Treatment Difference (IVA-Placebo) Through Week 8 for Change From Baseline in LCI2.5, FAS



Source: Figure 14.2.1.1
FAS: full analysis set; IVA: ivacaftor; LCI2.5: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. Repeated Measures Model: sequence by period by visit were cell effects with baseline LCI2.5 as a covariate; Covariance Structure=UN@CS; non-informative prior for cell effects and covariate effect; flat prior on variance-covariance parameters.

A supportive analysis of change from baseline in LCI2.5 through 8 weeks of treatment using a frequentist CI estimation approach based on MMRM is presented in Table 11-2. The LS mean of the average treatment difference through Week 8 between IVA and placebo groups in the change from baseline in LCI2.5 was -0.66 (95% CI: -1.10, -0.21).

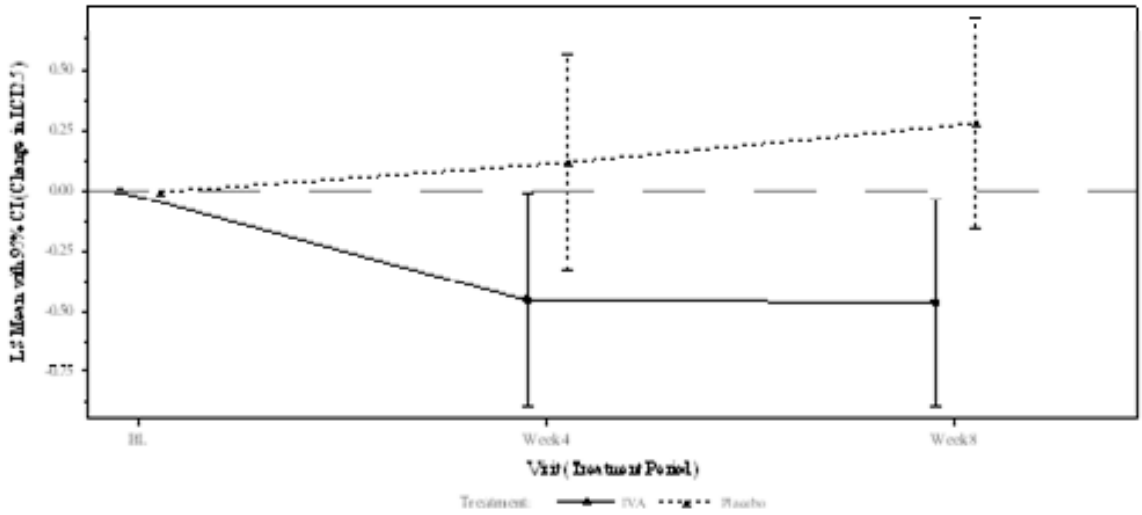
Table 11-2 MMRM Analysis of Change From Baseline in $LCI_{2.5}$ Through Week 8, FAS

	Placebo N = 38	IVA N = 38
Baseline		
n	38	
Mean (SD)	12.96 (4.74)	
Change from baseline through Week 8		
n	37	37
LS Mean (SE)	0.20 (0.19)	-0.46 (0.19)
95% CI of LS Mean	(-0.17, 0.57)	(-0.83, -0.09)
LS Mean Diff, 95% CI	NA	-0.66 (-1.10, -0.21)

Source: Table 14.2.1.3.1
CI: confidence interval; DF: degrees of freedom; Diff: difference; FAS: full analysis set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; SD: standard deviation; SE: standard error
Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. MMRM model: treatment, visit (period), treatment*visit (period), and period were fixed effects, with baseline $LCI_{2.5}$ as a covariate; Covariance Structure=UN@CS, DF=Kenward-Roger.

The LS mean change from baseline in LCI2.5 by visit is shown in Figure 11-2. Improvements in LCI2.5 were observed by Week 4 and sustained through Week 8 for the IVA group compared to placebo.

Figure 11-2 LS Mean Change From Baseline in LCI2.5 by Visit, FAS



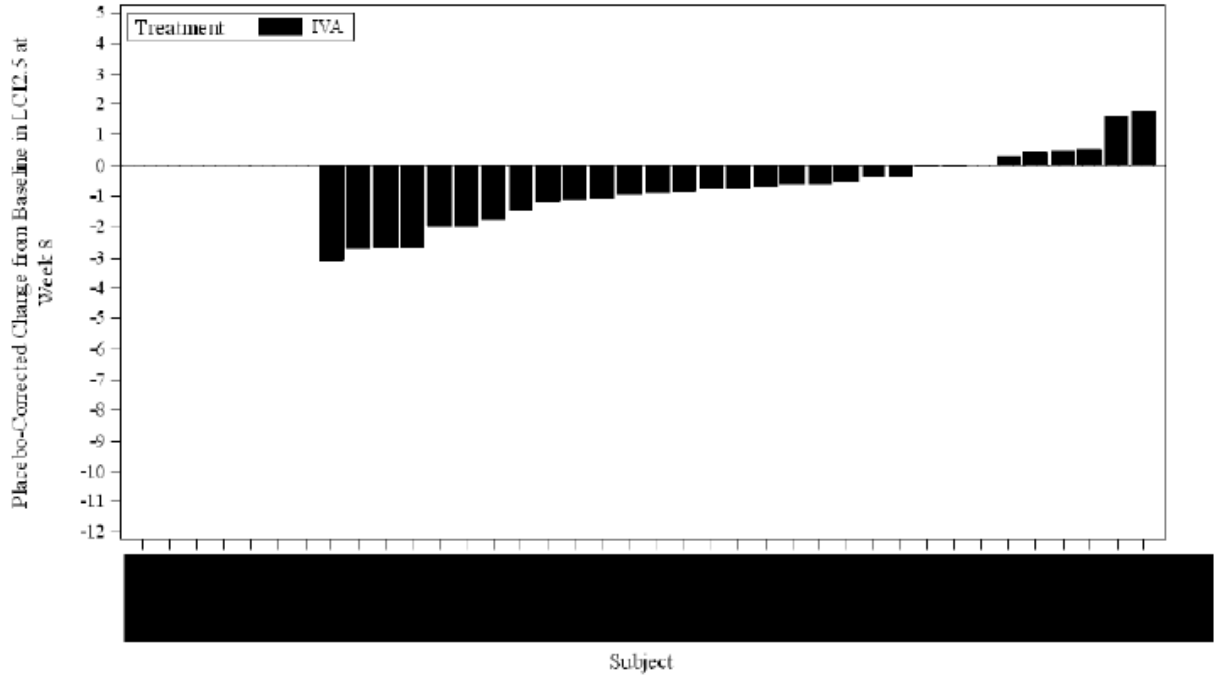
Source: Figure 14.2.1.2

BL: baseline; DF: degrees of freedom; IVA: ivacaftor; LS: least square; FAS: full analysis set; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value

Note: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. MMRM model: treatment, visit (period), treatment*visit (period), and period were fixed effects, with baseline $LCI_{2.5}$ as a covariate; Covariance Structure=UN@CS, DF=Kenward-Roger.

To evaluate individual response to IVA, a waterfall plot showing the subject-level placebo corrected change in LCI2.5 from study baseline at Week 8 is presented in Figure 11-3. The majority of subjects had improvements in placebo-corrected LCI2.5 at Week 8 of IVA treatment.

Figure 11-3 Waterfall Plot of Placebo-corrected Change From Study Baseline in LCI2.5 at Week 8 on IVA, FAS



Source: Figure 14.2.1.3
BL: baseline; IVA: ivacaftor; FAS: full analysis set; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. Each bar represents a subject treated in both treatment periods. Seven subjects did not have endpoint values at baseline or Week 8 in either IVA or placebo treatment periods. Placebo-corrected change from baseline values were calculated as change from baseline value for IVA – change from baseline value for placebo.

CHMP comment

The primary efficacy endpoint was the absolute change from baseline in $LCI_{2.5}$ through 8 weeks of treatment. The posterior mean is -0.68 with a Credible Interval of (-0.91; -0.45) and the Posterior probability that average treatment difference through 8 (IVA-Placebo) <0 is 99.76%. It implies that the probability of the difference between arms is greater than 0 is just 0.24% which is positive to the objective of the study.

As supportive analysis for this endpoint, the MMRM with a frequentist approach is presented by the MAH. The LS mean of the average treatment difference through Week 8 between IVA and placebo groups in the change from baseline in $LCI_{2.5}$ was -0.66 (95% CI: -1.10, -0.21). The upper interval is lower than 0 so it suggests that the difference between arms is significant in favour of the IVA arm.

The evidence shown by the MAH is consistent from a Bayesian approach and a frequentist approach (MMRM) and statistical significance seems to be met according to the results presented.

Nevertheless, the reduction in $LCI_{2.5}$ seems small. It has to be acknowledged that there are limited data from trials using this endpoint and the minimal clinically important difference has not yet been defined. But compared to the effect observed in patients with a G551D-CFTR mutation treated with ivacaftor for whom the difference in $LCI_{2.5}$ versus placebo was -2·16 [95% CI -2·88 to -1·44]; p<0·0001) [Davis J et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. Lancet Respir Med. 2013 Oct;1(8):630-638] the effect size looks very modest.

Subgroup analysis including LS mean and 95% CI are presented in Table 11-3.

Table 11-3 Subgroup Analysis: MMRM Analysis of Change From Baseline in Lung Clearance Index (LCI2.5) Through Week 8, FAS

	Placebo N = 38	IVA N = 38
ppFEV$_1$ at Baseline (<60) [1]		
n	9	10
LS Mean (SE)	0.01 (0.50)	-1.18 (0.47)
95% CI of LS Mean	(-1.05, 1.06)	(-2.19, -0.17)
LS Mean Diff, 95% CI	-	-1.19 (-2.42, 0.04)
ppFEV$_1$ at Baseline (≥60) [2]		
n	28	27
LS Mean (SE)	0.30 (0.20)	-0.27 (0.20)
95% CI of LS Mean	(-0.10, 0.69)	(-0.67, 0.13)
LS Mean Diff, 95% CI	-	-0.57 (-1.07, -0.06)
***CFTR* genotype for Mutation 1 (*3849 + 10KB C→T*) [3]**		
n	21	22
LS Mean (SE)	0.17 (0.28)	-0.38 (0.28)
95% CI of LS Mean	(-0.40, 0.75)	(-0.94, 0.18)
LS Mean Diff, 95% CI	NA	-0.56 (-1.21, 0.10)
***CFTR* genotype for Mutation 1 (*D1152H*) [4]**		
n	16	15
LS Mean (SE)	0.32 (0.20)	-0.61 (0.21)
95% CI of LS Mean	(-0.10, 0.74)	(-1.04, -0.17)
LS Mean Diff, 95% CI	NA	-0.93 (-1.51, -0.34)

Source: Table 14.2.1.4

CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; CI: confidence interval; DF: degrees of freedom; Diff: difference; FAS; full analysis set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; NA: not applicable; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SE: standard error

Notes: Baseline is study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. MMRM Model: treatment, visit (period), treatment*visit (period), and period are fixed effects, with baseline LCI2.5 as a covariate; Covariance Structure=UN@CS, DF=Kenward-Roger.

CHMP comment

Subgroup analyses for the change from baseline in $LCI_{2.5}$ through week 8 are shown in table below. Numerical advantage seems to favour IVA in all subgroups. However, due to the small sample sizes the results need to be interpreted with caution.

Other efficacy endpoints

LCI5.0

The results of the MMRM analysis of change from baseline in LCI5.0 (calculated as lung volume turnovers required to reach 1/20 of the starting N2 concentration) through 8 weeks of treatment is

presented in Table 11-4. The LS mean of the average treatment difference through Week 8 between IVA and placebo groups in the change from baseline in LCI5.0 was -0.28 (95% CI: -0.48, -0.08) which represented an improvement in LCI5.0 with 8 weeks of IVA treatment compared to placebo.

Table 11-4 MMRM Analysis of Change From Baseline in Lung Clearance Index (LCI5.0) Through Week 8, FAS

	Placebo N = 38	IVA N = 38
Baseline		
n	38	
Mean (SD)	7.73 (2.15)	
Change from baseline through Week 8		
n	37	37
LS Mean (SE)	0.13 (0.09)	-0.16 (0.09)
95% CI of LS Mean	(-0.06, 0.32)	(-0.34, 0.03)
LS Mean Diff, 95% CI	NA	-0.28 (-0.48, -0.08)

Source: Table 14.2.1.5.1

CI: confidence interval; DF: degrees of freedom; Diff: difference; FAS: full analysis set; IVA: ivacaftor; $LCI_{5.0}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; N: total sample size; NA: not applicable; SD: standard deviation; SE: standard error

Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. MMRM model: treatment, visit (period), treatment*visit (period), and period were fixed effects, with baseline $LCI_{5.0}$ as a covariate; Covariance Structure=UN@CS, DF=Kenward-Roger.

CHMP comment

As previously mentioned, $LCI_{5.0}$ measures the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value (as compared with 1/40th for $LCI_{2.5}$). It is a less stringent endpoint but therefore more sensitive to a placebo effect. The treatment difference from placebo is therefore consistent and reassuring although the effect is small.

Sweat chloride

The results of the MMRM analysis of the change from baseline in sweat chloride through 8 weeks of treatment are shown in Table 11-5. The LS mean of the average treatment difference through Week 8 between IVA and placebo groups in the change from baseline in sweat chloride was -9.2 mmol/L (95% CI: -12.4, -5.9), which represented an improvement in sweat chloride with IVA treatment compared to placebo.

Table 11-5 MMRM Analysis of Change From Baseline in Sweat Chloride (mmol/L) Through Week 8, FAS

Visit	Statistic	Placebo N = 38	IVA N = 38
Baseline	n	38	
	Mean (SD)	49.1 (24.0)	
Change from baseline through Week 8	n	38	36
	LS Mean (SE)	-0.1 (1.2)	-9.3 (1.2)
	95% CI of LS Mean	(-2.4, 2.3)	(-11.7, -6.8)
	LS Mean Diff, 95% CI	NA	-9.2 (-12.4, -5.9)

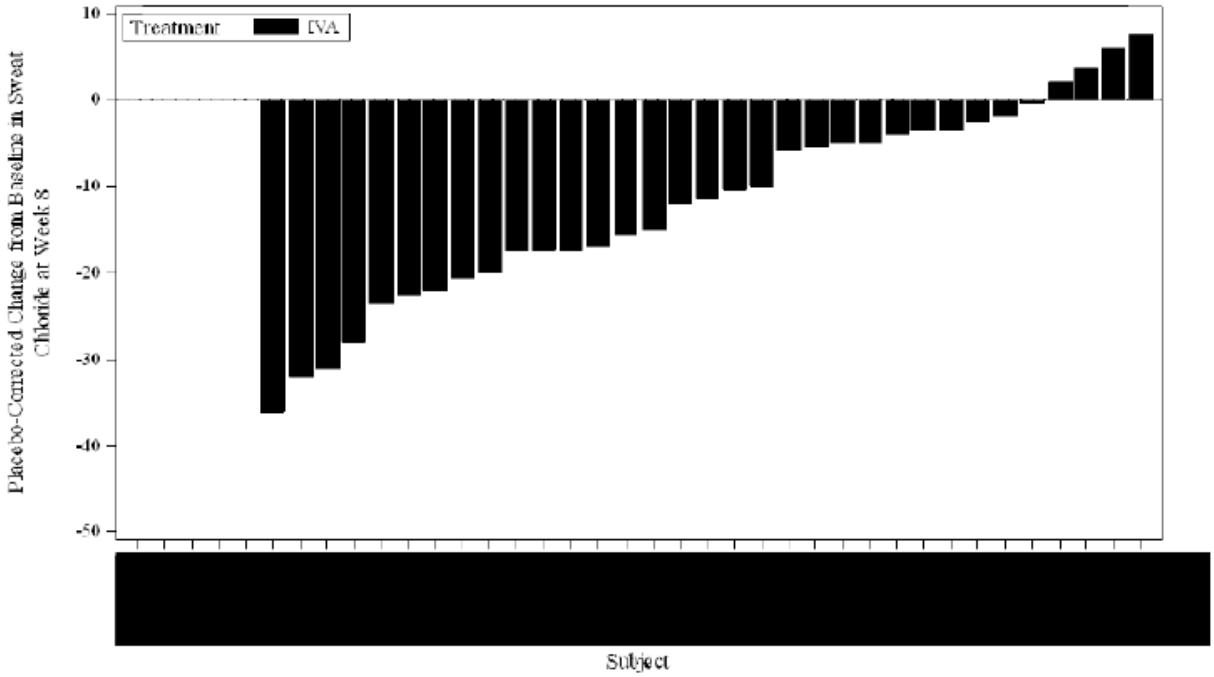
Source: Table 14.2.2.2.1

CI: confidence interval; DF: degrees of freedom; Diff: difference; FAS: full analysis set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; NA: not applicable; SD: standard deviation; SE: standard error

Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug for Treatment Period 1. MMRM model: treatment, visit (period), treatment*visit (period), and period were fixed effects, with baseline sweat chloride as a covariate; Covariance Structure=UN@CS, DF=Kenward-Roger.

The placebo-corrected change from baseline in sweat chloride at Week 8 for individual subjects treated with IVA is presented as a waterfall plot in Figure 11-5. The majority of subjects on IVA with paired sweat chloride measurements had a placebo-corrected change from baseline of at least -10 mmol/L by Week 8.

Figure 11-5 Waterfall Plot of Placebo-corrected Change From Baseline in Sweat Chloride (mmol/L) at Week 8 on IVA, FAS



Source: Figure 14.2.3.2

FAS: full analysis set; IVA: ivacaftor

Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. Each bar represents a subject treated in both treatment periods. Placebo-corrected change from baseline values were calculated as change from baseline value for IVA minus change from baseline value for placebo.

CHMP comment

The change from baseline in sweat chloride compared to placebo was -9.2 (-12.4, -5.9) with patients on placebo remaining virtually equal compared to their baseline value. The effect seems related to kalydeco administration and could be reflecting the restoration of the biochemical defect with ivacaftor administration. However, the effect size is not as large as the one seen in other mutations. The waterfall plot shows that almost all patients on IVA had a reduction in sweat chloride levels. For some of them the reduction versus placebo was higher than 10 mmol/L.

CFQ-R

The results of the MMRM analysis of the change from baseline by visit in CFQ-R RD score at Week 8 of treatment are shown in Table 11-6. At Week 8, the LS mean change from study baseline in CFQ-R RD score was -1.7 for subjects receiving placebo and +17.1 for subjects receiving IVA. The LS mean of the treatment difference at Week 8 between IVA and placebo groups in the change from baseline in CFQ-R RD was +18.7 (95% CI: 12.5, 25.0), which represented a substantial improvement in CFQ-R RD score with IVA treatment compared to placebo.

Table 11-6 MMRM Analysis of Change From Baseline in CFQ-R RD Score - At Week 8, FAS

Visit	Statistic	Placebo N = 38	IVA N = 38
Baseline	n	38	
	Mean (SD)	62.3 (20.3)	
Change from baseline at Week 8	n	38	37
	LS Mean (SE)	-1.7 (2.3)	17.1 (2.4)
	95% CI of LS Mean	(-6.3, 3.0)	(12.4, 21.8)
	LS Mean Diff, 95% CI	NA	18.7 (12.5, 25.0)

Source: Table 14.2.3.2

FAS: full analysis set; CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; DF: degrees of freedom; Diff: difference; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; N: total number of subjects; n: number of subjects; NA: not applicable; RD: Respiratory Domain; SD: standard deviation; SE: standard error

Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug for Treatment Period 1. MMRM model: treatment, and period are fixed effects, with baseline CFQ-R respiratory domain score as a covariate; Covariance Structure=UN, DF=Kenward-Roger.

CHMP comments

An important increase in CFQ-R respiratory domain at week 8 compared to placebo is reported (+18.7). This improvement is impressive and somehow unexpected considering the limited size effect on other clinical endpoints and relevant parameters.

ppFEV1

The results of the MMRM analysis of the absolute change from baseline in ppFEV1 through 8 weeks of treatment are shown in Table 11-7. The LS mean of the average treatment difference through Week 8 between IVA and placebo groups in the absolute change from baseline in ppFEV1 was +2.7 percentage points (95% CI: 0.6, 4.7) and represented an improvement in ppFEV1 with IVA treatment compared to placebo.

Table 11-7 MMRM Analysis of Absolute Change From Baseline in ppFEV$_1$ Through Week 8, FAS

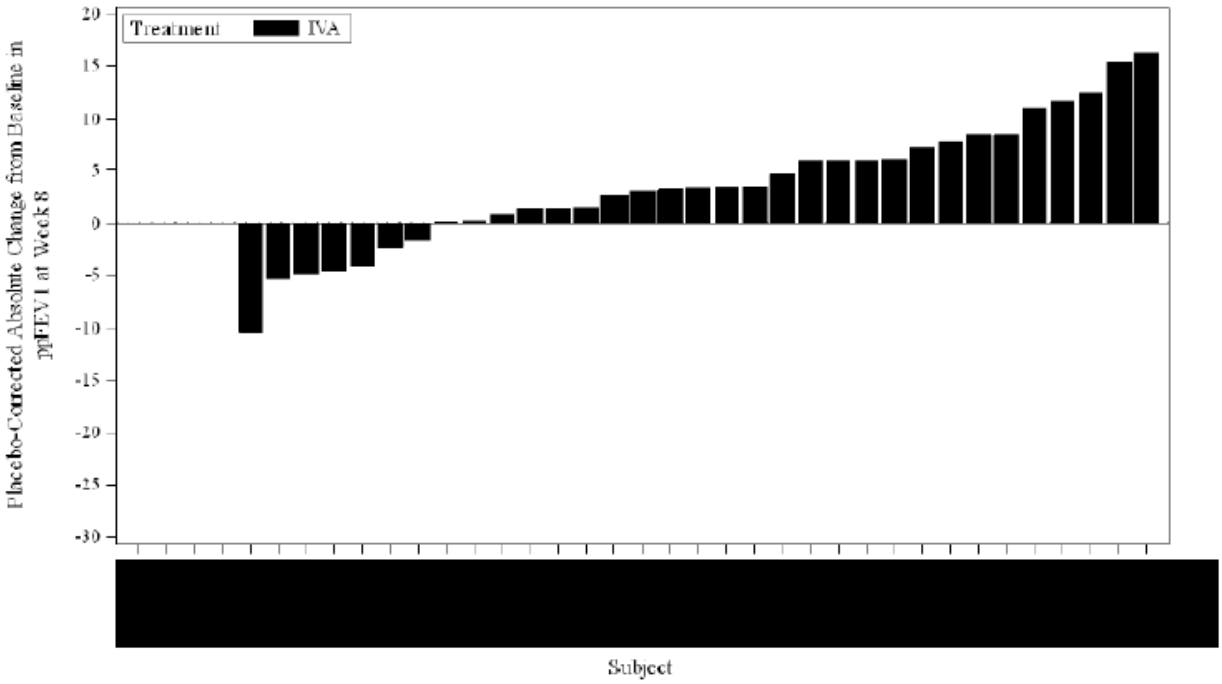
Visit	Statistic	Placebo N = 38	IVA N = 38
Baseline	n	38	
	Mean (SD)	74.0 (16.9)	
Absolute Change from baseline through Week 8	n	36	38
	LS Mean (SE)	-0.5 (0.8)	2.2 (0.8)
	95% CI of LS Mean	(-2.1, 1.2)	(0.6, 3.8)
	LS Mean Diff, 95% CI	NA	2.7 (0.6, 4.7)

Source: Table 14.2.4.2.1

CI: confidence interval; DF: degrees of freedom; FAS: full analysis set; n: number of subjects; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; N: total sample size; n: size of subsample; NA: not applicable; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SD: standard deviation; SE: standard error

Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug for Treatment Period 1. MMRM model: treatment, visit (period), treatment*visit (period), and period were fixed effects, with baseline ppFEV$_1$ as a covariate; Covariance Structure=UN@CS, DF=Kenward-Roger.

Waterfall Plot of Placebo-corrected Absolute Change From Baseline in ppFEV$_1$ (Percentage Points) at Week 8 on IVA, FAS



FAS: full analysis set; IVA: ivacaftor; ppFEV$_1$: percent predicted forced expiratory volume in 1 second;

Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. Each bar represents a subject treated in both treatment periods. Placebo-corrected absolute change from baseline values were calculated as absolute change from baseline value for IVA minus absolute change from baseline value for placebo.

CHMP comment

Spirometry was also performed in this trial in order to assess the change in ppFEV1 at week 8. A slight reduction was observed in patients on placebo while an increase was seen in patients treated with ivacaftor. This increase was small (+2.7) compared to that seen in other studies in which IVA was

given to CF patients with different mutations. An (modest) increase was seen in most patients (waterfall plot).

A subgroup analysis including LS mean and 95% CI is presented in Table 11-8. Subgroup results are based on small sample sizes and should be interpreted with caution

Table 11-8 Subgroup Analysis: MMRM Analysis of Absolute Change From Baseline in ppFEV$_1$ (Percentage Points) Through Week 8, FAS

	Placebo N = 38	IVA N = 38
ppFEV$_1$ at Baseline (<70) [1]		
n	18	18
LS Mean (SE)	0.5 (1.1)	4.6 (1.1)
95% CI of LS Mean	(-1.7, 2.8)	(2.3, 6.9)
LS Mean Diff, 95% CI	NA	4.1 (1.5, 6.6)
ppFEV$_1$ at Baseline (≥70 and ≤90) [2]		
n	11	11
LS Mean (SE)	-1.4 (1.6)	-0.1 (1.6)
95% CI of LS Mean	(-4.7, 1.9)	(-3.4, 3.2)
LS Mean Diff, 95% CI	NA	1.3 (-4.0, 6.7)
ppFEV$_1$ at Baseline (>90) [3]		
n	7	9
LS Mean (SE)	-2.5 (2.2)	0.5 (2.0)
95% CI of LS Mean	(-7.3, 2.2)	(-3.8, 4.8)
LS Mean Diff, 95% CI	NA	3.0 (-2.5, 8.6)
***CFTR* genotype for Mutation 1 (*3849 + 10KB C→T*) [4]**		
n	21	22
LS Mean (SE)	-1.1 (1.0)	2.4 (1.0)
95% CI of LS Mean	(-3.0, 0.9)	(0.5, 4.3)
LS Mean Diff, 95% CI	NA	3.5 (1.0, 6.0)
***CFTR* genotype for Mutation 1 (*D1152H*) [5]**		
n	15	16
LS Mean (SE)	1.3 (1.5)	1.2 (1.5)
95% CI of LS Mean	(-1.9, 4.4)	(-1.8, 4.3)
LS Mean Diff, 95% CI	NA	-0.1 (-4.3, 4.1)

Source: Table 14.2.4.3

CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; CI: confidence interval; DF: degrees of freedom; FAS; full analysis set; n: size of subsample; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; NA: not applicable; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SE: standard error

Notes: Baseline was study baseline defined as the most recent non-missing measurement before the first dose of study drug in Treatment Period 1. MMRM Model: treatment, visit (period), treatment*visit (period), and period were fixed effects, with baseline ppFEV1 as a covariate; Covariance Structure=UN@CS, DF=Kenward-Roger.

CHMP comments

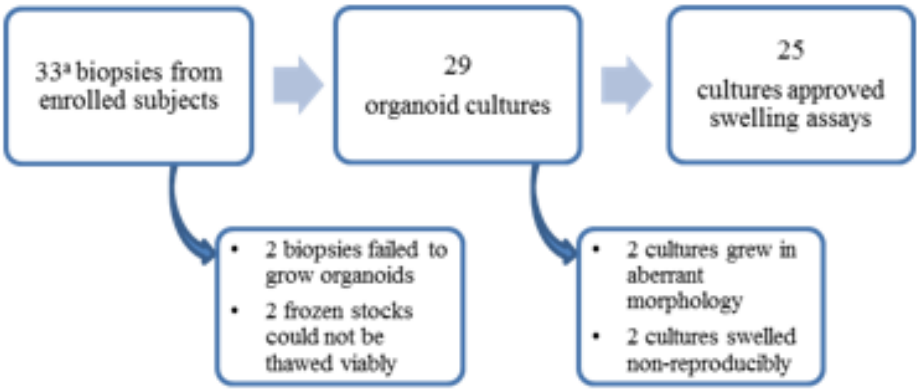
Small changes in ppFEV1 are seen in all subgroups. However, the low number of patients in each subset makes it difficult to interpret the results.

Organoid-based Measurements

Intestinal-like organoid swelling is a measure of CFTR function in vitro. In this assay 5 different forskolin concentrations and six VX-770 concentrations were tested, for a total of thirty experimental conditions for the assay.

In all patient derived organoid cultures, some level of swelling was observed (maximum swelling over all conditions 151%-295%). Twenty nine organoid cultures were successfully established from 33 rectal biopsies. Four organoid cultures were lost due to failure to meet quality control standards, resulting in 25 viable organoids for the planned assays, representing 25 subjects (Figure 11-8).

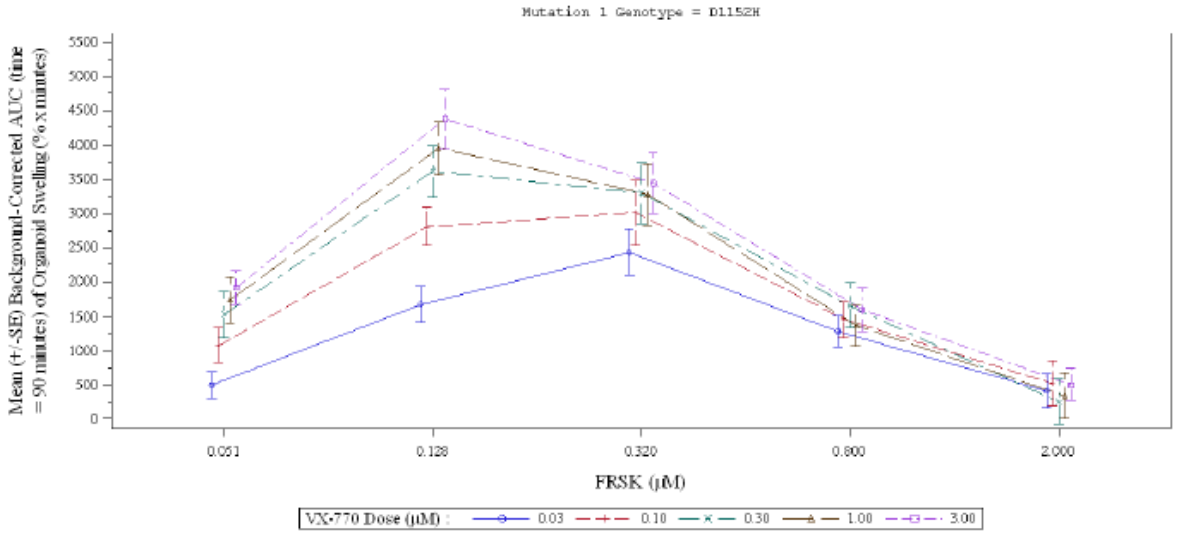
Figure 11-8 Flowchart Depicting an Overview of all Biopsies, Organoid Cultures, and Assays Performed



Source: Report P121, Figure 2

[a] One subject had a biopsy at screening, but the subject was not enrolled. Therefore, 34 total biopsies were generated, but only 33 organoids were generated from enrolled subjects.

Dose-response curves for organoid-based measurements are shown in Figure 11-9 (AUC of organoid swelling) and Figure 11-10 (maximum value of organoid swelling). The VX-770 effect was most pronounced when the organoids were treated with 0.128 µM FRSK. Organoids established from subjects with either CFTR mutation (3849 + 10KB C→T or D1152H) displayed dose-dependent swelling with VX-770 treatment.



Source: Figure 14.2.4.2
FAS: full analysis set; FRSK: forskolin; SE: standard error
Note: Each point represents the average background-corrected maximum organoid swelling at corresponding FRSK and VX-770 concentrations.

A Pearson correlation analysis was performed on background-corrected organoid swelling versus placebo-corrected change from study baseline at Week 8 of IVA treatment for each of the clinical endpoints (LCI2.5, ppFEV1, and sweat chloride) at each experimental condition corresponding to different FRSK and VX-770 concentrations. The in vitro organoid-based assay performed as expected with VX-770 treatment associated with increased organoid swelling.

Organoids from both mutations demonstrated a response to VX-770, however no evidence of correlation was observed between the degree of organoid swelling and the degree of response in clinical endpoints. Pearson correlations of organoid swelling following treatment with 0.128 µM FRSK and 0.3 µM VX-770 are presented in Table 11-9 (AUC of Organoid Swelling) and Table 11-10 Maximum Organoid Swelling) because these experimental conditions provided the greatest window to detect a correlation.

Table 11-9 Pearson Correlation Between Background-corrected AUC of Organoid Swelling and Placebo-corrected Change from Baseline in Clinical Endpoint at Week 8 of IVA Treatment by Genotype and Experiment Condition, FAS

		Genotype for Mutation 1	
Clinical Endpoint	**Statistic**	***3849 + 10KB C→T***	***D1152H***
$LCI_{2.5}$			
	n	13	8
	Pearson Correlation	-0.4383	0.5316
	P value	0.1341	0.1751
Sweat Chloride			
	n	14	8
	Pearson Correlation	-0.3335	0.2098
	P value	0.2440	0.6180
$ppFEV_1$			
	n	14	7
	Pearson Correlation	-0.0701	-0.2251
	P value	0.8118	0.6274

Sources: Table 14.2.8.5, Table 14.2.8.6, Table 14.2.8.7
AUC: area under the curve; FAS: full analysis set; FRSK: forskolin; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second
Notes: Experiment condition: 0.128 µM FRSK, 3 µM VX-770. Background-corrected AUC Time: 90 minutes, organoid swelling: % × minutes. Background corrected values were calculated as the difference in swelling for (FRSK+VX-770) versus (FRSK alone). Placebo-corrected change from baseline values were calculated as change from baseline value for IVA minus change from baseline value for placebo.

Table 11-10 Pearson Correlation Between Background-corrected Maximum Organoid Swelling and Placebo-corrected Change From Baseline in Clinical Endpoint at Week 8 of IVA Treatment by Genotype and Experiment Condition, FAS

Clinical Endpoint	Statistic	Genotype for Mutation 1	
		3849 + 10KB C→T	*D1152H*
$LCI_{2.5}$			
	n	13	8
	Pearson Correlation	-0.4318	0.4905
	P value	0.1407	0.2172
Sweat Chloride			
	n	14	8
	Pearson Correlation	-0.3222	-0.0009
	P value	0.2613	0.9983
$ppFEV_1$			
	n	14	7
	Pearson Correlation	-0.1034	-0.3142
	P value	0.7251	0.4925

Sources: Table 14.2.8.8, Table 14.2.8.9, Table 14.2.8.10

FAS: full analysis set; FRSK: forskolin; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

Notes: Experiment condition: 0.128 µM FRSK, 3 µM VX-770. Background-corrected maximum organoid swelling: %. Background corrected values were calculated as the difference in swelling for (FRSK+VX-770) versus (FRSK alone). Placebo-corrected change from baseline values were calculated as change from baseline value for IVA minus change from baseline value for placebo.

CHMP comments

The MAH has used also the intestinal organoids to assess the efficacy of ivacaftor in patients carrying 3849 + 10KB C→T or D1152H CFTR mutations. This methodology is a promising tool that might have a place in the assessment of very rare mutations that can be studied in clinical trials. Nevertheless, it is not validated yet for regulatory purposes.

In this study, biopsies of thirty-four patients were used for that purpose. Two of them did not generate organoids and another two organoids failed to recover after thawing. Analysis of the other 26 organoid lines in the FIS assays showed swelling of most organoid lines although 2 out of the 14 carrying a 3849+10kbC->T CFTR allele had a lower response than the average. All organoid cultures carrying a D1152H allele showed significant swelling when exposed to VX-770 (n=12). In most organoid cultures swelling was observed at high forskolin concentrations (0.32, 0.8 and 2 µM) in the absence of VX-770 suggesting that these mutations retain some function.

According to the MAH, studies performed in the past with organoids carrying gating mutations showed reproducible organoid swelling in response to VX-770 treatment that correlated with clinical benefit. In this particular case, although organoids from both mutations demonstrated a response to ivacaftor there is no evidence of correlation between the degree of organoid swelling and the degree of response in clinical endpoints.

The MAH has provided additional information about the mutation in the second allele in 34 patients. Most subjects with the 3849+10kbC->T mutation (n=19) had the W1282X mutation (n=12) or the F508del (n=5) in the second allele. According to the CFTR2 database these variant combinations causes CF. Patients with CF who have these variants are likely to be pancreatic sufficient. Most patients with the D1152H mutation (n=15) had also the W1282X mutation (n=5) or the F508del (n=4) in the second allele. According to the CFTR2 database, these variant combinations have varying consequences so some patients have CF and some do not. Patients with CF who have this variant are likely to be pancreatic sufficient.

Change from Baseline in Weight, Height, and BMI

No trends were identified in the change from baseline in weight, height, or BMI, or weight-, height-, or BMI-forage z scores (for subjects <21 years of age) between the 2 treatment groups.

Pulmonary Exacerbations

There were 2 PEx in 2 subjects; 1 subject receiving placebo and 1 subject receiving IVA.

CHMP comments

Two patients, one in placebo and one in ivacaftor group had a pulmonary exacerbation.

SAFETY RESULTS

Extent of Exposure

The extent of exposure to study drug (IVA or placebo) is summarized in Table 12-1.

Table 12-1 Study Drug Exposure, Safety Set

	Placebo N = 38	IVA N = 38
Total exposure (patient weeks)	310.9	308.1
Exposure Duration (weeks)		
n	38	38
Mean (SD)	8.2 (0.3)	8.1 (0.4)
SE	0.1	0.1
Median	8.1	8.1
Min, Max	7.3, 8.9	6.3, 8.9
Exposure duration by interval, n (%)		
≤2 weeks	0	0
>2 and ≤4 weeks	0	0
>4 and ≤8 weeks	8 (21.1)	8 (21.1)
>8 weeks	30 (78.9)	30 (78.9)

Source: Table 14.1.7

IVA: ivacaftor; max: maximum value; min: minimum value; n: size of subsample; N: total sample size; SD: standard deviation; SE: standard error

Note: Duration of study drug exposure (weeks) = (last dose date - first dose date + 1) /7, regardless of any interruptions in dosing.

CHMP comments

The mean exposure duration was similar for placebo (8.2 weeks) and IVA (8.1 weeks) groups.

Adverse Events

Adverse event summary tables include TEAEs only. TEAEs will hereafter be referred to as AEs. AEs that started (or increased in severity) during a specific treatment (IVA or placebo) were summarized under the study drug the subject received during that treatment. AEs that started (or increased in severity) during the Washout Period were summarized under the study drug received in Treatment Period 1.

An overview of AEs is presented in Table 12-2

Table 12-2 Integrated Summary of AEs, Safety Set

Category	Placebo N = 38 n (%)	IVA N =38 n (%)
Number of AEs (Total)	50	34
Subjects with any AE	22 (57.9)	22 (57.9)
Subjects with AEs by strongest relationship		
Not Related	20 (52.6)	19 (50.0)
Unlikely Related	1 (2.6)	3 (7.9)
Possibly Related	1 (2.6)	0
Related	0	0
Subjects with AEs by maximum severity		
Mild	13 (34.2)	10 (26.3)
Moderate	7 (18.4)	5 (13.2)
Severe	2 (5.3)	7 (18.4)
Life threatening	0	0
Missing	0	0
Subjects with AE leading to treatment discontinuation	0	0
Subjects with AE leading to study drug interruption	1 (2.6)	1 (2.6)
Subjects with serious AEs	2 (5.3)	1 (2.6)

Source: Table 14.3.1.1

AE: adverse event; IVA: Ivacaftor; n: size of subsample; N: total sample size

Notes: MedDRA version 20.0. 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. An AE with relationship missing is counted as Related.

The AEs with an incidence of at least 5% of subjects in either treatment group are presented by SOC and PT in Table 12-3. The SOC (≥30% incidence in any group) with the highest incidence of AEs in both treatment groups was infections and infestations.

In both treatment groups, most AEs were consistent with common manifestations of CF. By PT, the most common AEs (≥10% incidence in any group) were infective PEx of CF, upper respiratory tract infection, and viral upper respiratory tract infection.

Table 12-3 AEs Occurring in At Least 5% of Subjects in Any Treatment Group by System Organ Class and Preferred Term, Safety Set

System Organ Class Preferred Term	Placebo N = 38 n (%)	IVA N = 38 n (%)
Any adverse event	22 (57.9)	22 (57.9)
Infections and infestations	15 (39.5)	13 (34.2)
Infective pulmonary exacerbation of cystic fibrosis	2 (5.3)	5 (13.2)
Upper respiratory tract infection	6 (15.8)	3 (7.9)
Viral upper respiratory tract infection	9 (23.7)	1 (2.6)
Respiratory, thoracic and mediastinal disorders	5 (13.2)	4 (10.5)
Haemoptysis	2 (5.3)	3 (7.9)
Gastrointestinal disorders	4 (10.5)	2 (5.3)
Aphthous ulcer	2 (5.3)	0
General disorders and administration site conditions	3 (7.9)	2 (5.3)
Pyrexia	1 (2.6)	2 (5.3)
Malaise	2 (5.3)	0
Nervous system disorders	2 (5.3)	1 (2.6)
Headache	2 (5.3)	1 (2.6)

Sources: Table 14.3.1.2 and Table 14.3.1.3
AE: adverse event; IVA: Ivacaftor; n: size of subsample; N: total sample size
Notes: MedDRA version 20.0. A subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of IVA column by System Organ Class, and by Preferred Term within each SOC.

Severity of Adverse Events

A summary of the severity of AEs is presented in Table 12-2. If a subject had more than 1 occurrence of an AE, the AE with the highest severity was included. The majority of subjects had AEs that were mild (60.5%) or moderate (31.6%) in severity. Of the 22 subjects with AEs in the IVA group, 10 (26.3%) subjects had mild AEs, 5 (13.2%) subjects had moderate AEs, and 7 (18.4%) had severe AEs. Of the 22 subjects with AEs in the placebo group, 13 (34.2%) subjects had mild AEs, 7 (18.4%) subjects had moderate AEs, and 2 (5.3%) subjects had severe AEs. Overall, the incidence of mild and moderate AEs was lower in the IVA group compared to placebo.

The severe AEs in the IVA group included headache, influenza, upper respiratory tract infection, constipation, forced expiratory volume decreased, infective PEx of CF, and rash. The severe AEs in the placebo group included pancreatitis, myalgia, and allergy to animal. None of the severe AEs were considered related to study drug treatment.

CHMP comments

Only TEAEs are shown in this application. In both placebo and ivacaftor groups 57.9 % of patients had at least one TEAE. Most of them were considered not related and only 2 patients on placebo (5.3%) and 7 on ivacaftor (18.4%) had a severe AE.

The most frequent TEAEs were infections and infestations, in particular of the respiratory tract that it is expected in this CF population, followed by respiratory, thoracic, and mediastinal disorders.

Deaths

There were no deaths in this study.

Other Serious Adverse Events

Three (7.9%) subjects had SAEs: 1 subject in the IVA group had a spontaneous abortion, 1 subject in the placebo group had an infective PEx of CF, and 1 subject in the placebo group had pancreatitis. All events were considered unlikely or unrelated to study drug.

Adverse Events That Led to Discontinuation of Study Drug or That Led to Interruption of Study Drug

There were no AEs that led to treatment discontinuation in this study. Two (5.3%) subjects had AEs that led to treatment interruption in this study: 1 subject in the IVA group who had an AE of rash and 1 subject in the placebo group who had an SAE of pancreatitis. Both AEs were considered not related or unlikely related to study drug.

CHMP comments

One patient reported rash, an AE that it is already described in the SmPC as a very common AE.

Clinical Laboratory Evaluation

Liver Function Test

There were mean decreases from baseline at Week 8 in amylase and lipase values in the IVA group (Table 12-4). In addition, there were more subjects with high lipase values that normalized by Week 8 of treatment in the IVA group compared to placebo.

Table 12-4 Amylase and Lipase Parameters: Changes From Baseline at Week 8, Safety Set

	Placebo N = 38				IVA N = 38			
	Change from baseline				Change from baseline			
Parameter	n	Mean (SD)	Median	Min, Max	n	Mean (SD)	Median	Min, Max
Amylase (U/L)	38	2.0 (10.4)	0.5	-13, 37	38	-21.8 (28.5)	-13.5	-146, 13
Lipase (U/L)	38	0.66 (14.64)	0.00	-33.0, 38.0	38	-31.29 (52.24)	-13.50	-270.0, 23.0

Source: Table 14.3.4.1

IVA: ivacaftor; max: maximum value; min: minimum value; SD: standard deviation; n: size of subsample; N: total sample size

Note: Baseline is period baseline defined as the most recent non-missing measurement collected before the first dose of study drug in each Treatment Period.

The maximum on-treatment LFT results are presented in Table 12-5. The majority of subjects had maximum on-treatment ALT or AST $\leq 3 \times$ ULN. No clinically notable trends or safety concerns were identified.

Table 12-5 Maximum On-treatment LFT Results, Safety Set

Maximum On-treatment Result Threshold Analysis Criteria n/N1 (%)	Placebo N = 38	IVA N = 38
ALT (U/L)		
>ULN to ≤3 × ULN	2/37 (5.4)	2/38 (5.3)
>3 to ≤5 × ULN	1/37 (2.7)	0
AST (U/L)		
>ULN to ≤3 × ULN	3/38 (7.9)	2/38 (5.3)
ALT or AST (U/L)		
(ALT>ULN to ≤3 × ULN) or (AST>ULN to ≤3 × ULN)	4/38 (10.5)	3/38 (7.9)
(ALT>3 to ≤5 × ULN) or (AST>3 to ≤5 × ULN)	1/38 (2.6)	0
Total Bilirubin (µmol/L)		
>ULN to ≤1.5 × ULN	2/37 (5.4)	3/38 (7.9)
>1.5 to ≤2 × ULN	0	1/38 (2.6)

Source: Table 14.3.4.2

ALT: alanine transaminase; AST: aspartate transaminase; IVA: ivacaftor; LFT: liver function test; n: size of subsample; N: total sample size; ULN: upper limit of normal

Notes: For n, subject was only counted once in the worst category of all assessments during the TE period for each Treatment Period. N1 is the number of subjects with at least one non-missing measurement during the TE period for each Treatment Period. Criteria involving 2 LFT parameters were determined by assessments at different visits during the TE period for each Treatment Period.

CHMP comment

No patients had increases in transaminases above 8 x ULN. The incidence of ALT or AST levels >3 to < 5 x ULN was 2.6% in patients on placebo versus 0% in subjects on kalydeco. Overall, the percentage of patients with elevated transaminases was not very high. One patient on IVA had elevations of bilirrubin >1.5 to < 2 x ULN. The percentage of patients with >ULN to 1.5 x ULN was higher in patients receiving Kalydeco compared to placebo (7.9% versus 5.4%, respectively).

Mild hepatic transaminase elevation is a common occurrence in CF patients particularly among young children with cystic fibrosis. Elevated transaminases have been also reported in patients with CF receiving ivacaftor. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin.

A warning on the increase of transaminases in CF patients treated with ivacaftor is in section 4.4 of the SmPC.

Vital Signs (pag 74)

No clinically relevant trends or changes from baseline were observed during either treatment period for HR, temperature, respiratory rate, or blood pressure.

CHMP comments

There were no important findings in chemistry, haematology coagulation, urinalysis and vital signs.

Cataract opacity

No cataracts or lens opacities were observed during either treatment period.

2.3.3. Discussion on clinical aspects

Study 127 is submitted as a stand-alone post-authorization measure (PAM) under Article 46 of Regulation (EC) No 1901/2006 (the "Paediatric Regulation"). This study was designed to evaluate the efficacy of ivacaftor treatment in subjects with cystic fibrosis (CF) 6 years of age and older who have a 3849 + 10KB C→T or D1152H-CFTR mutation.

Both are mutations of low prevalence that may cause disease that it is in general of mild to moderate severity. Some subjects with D1152H may be asymptomatic.

Study 127 included male and female subjects 6 years of age and older weighing ≥25 kg with confirmed diagnosis of CF, and a 3849 + 10KB C→T or D1152H-CFTR mutation on at least 1 allele, and forced expiratory volume in 1 second (FEV1) ≥40% of predicted and ≤105% of predicted at screening.

The primary endpoint was the change in lung clearance index ($LCI_{2.5}$). As lung disease usually evolves slowly this index, that measures the degree of small airway disease by assessing ventilation inhomogeneity, may be useful in young CF patients with spirometry apparently normal. $LCI_{2.5}$ is more likely to reveal differences in ventilation homogeneity than $LCI_{5.0}$ since while $LCI_{2.5}$ measures the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value, $LCI_{5.0}$ measures the number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value.

Although the experience with LCI in the assessment of lung function in CF patients is still limited and it is somehow unknown the change from baseline that can be considered clinically relevant, the use of LCI as the primary endpoint is acceptable provided that the results are supported by evidence of clinical relevance from other endpoints.

Additional endpoints were the absolute change from baseline in $LCI_{5.0}$ through 8 weeks, the change in ppFEV1, the change in CFQ-R and the change in sweat chloride. Organoid-based measurements of ivacaftor-induced CFTR function in vitro were also assessed as an additional endpoint. All are considered appropriate in this setting.

The sample size calculation has been focused on the precision to estimate the treatment difference through Week 8 in $LCI_{2.5}$ between IVA and placebo groups. 50 subjects were initially planned to participate in the study but instead, 38 have been randomized. The MAH should explain numerically how this reduction of the planned sample size affects to the precision calculated and to the results presented.

These baseline characteristics were very similar for the patients in both sequences. Slightly more subjects had the 3849+10kbC->T mutation (57.9%) compared to the D1152H mutation (42.1%). Most patients with the 3849+10kbC->T mutation had the W1282X mutation or the F508del in the second allele and according to the CFTR2 database these variant combinations cause CF although the subjects are likely to be pancreatic sufficient. Regarding subjects with the D1152H mutation most had the W1282X or the F508del mutation in the second allele. These variant combinations have varying consequences so some patients have CF and some do not. These subjects are likely to be pancreatic sufficient.

Baseline ppFEV1 was ≥40 and < 70% in around 50% of patients in both sequences. Twenty six percent (26.3%) and 31.6% had ppFEV ≥ 70 and ≤90 and 26.3% and 21.1% ppFEV1 >90% in sequences 1 and 2, respectively. $LCI_{2.5}$ at baseline was around 13 in both sequences with minimum values in some patients of 6.61 and 6.75 and maximum values of 21.36 and 25.47, respectively (normal value <7.5). This would be reflective of uneven ventilation and small airways disease in most of patients. In general, the patients seem to have a lung function moderately affected.

Sweat chloride was 41.5 and 52.0 mmol/L for patients on sequence 1 and 2 and minimum values of 18 and 12 mmol/L, respectively. Such low values, however, are not likely indicative of CF. It would have been desirable that a sweat chloride at baseline equal or above 60 mmol/l had been requested for all patients. The MAH should provide individual data of patients with sweat chloride values under 60 mmol/L and the corresponding mutation.

Patients with 3849 + 10KB C→T or D1152H-CFTR mutations are expected to be pancreatic sufficient. However, some cases of pancreatitis and pancreatic failure are described for some patients in both sequences (3 in sequence 1 and 1 in sequence 2) that could be indicative of pancreatic insufficiency.

Only 2 subjects were younger than 12 years of age in each sequence of treatment of study 127 but based on the data available it was unknown how many were adolescents. For the purpose of this application (submission of data under Art 46 of the "Paediatric Regulation") it is of interest to have the information on the paediatric population. For this purpose, the MAH was requested to provide their baseline characteristics including ppFEV1 (including categories <40; ≥40 and <70; ≥70 and ≤90; and >90); sweat chloride, LCi2.5, LCI5 and CFQR at baseline, and the genotype of each of them if the paediatric population (i.e., patients younger than 18 years of age) were a substantial proportion of the whole population (i.e., 50% or more). For all these parameters, the mean (SD), median, minimum and maximum values should be provided even when these values would have a purely descriptive interest.

In their responses the MAH explained that the percentage of children and adolescents was only 21% (8/38) of the study population. Given the small numbers, no sound conclusion is expected to be drawn from the efficacy and safety data of this subset. The MAH has not provided any data what it is considered acceptable.

Efficacy results

Efficacy results are presented only for the whole population.

Primary endpoint: absolute change from baseline in LCI2.5 compared to placebo at week 8.

The primary endpoint was met with a difference of -0.66 (95% CI: -1.10, -0.21) versus placebo. The reduction seems small. It is acknowledged that the minimal clinically important difference has not yet been defined for this endpoint but the effect size seems quite modest when compared with the one in CF patients with a G551D-CFTR mutation treated with ivacaftor (+2.16 [95% CI -2.88 to -1.44]; p<0.0001) [Davis J et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial. Lancet Respir Med. 2013 Oct;1(8):630-638].

Overall, the additional endpoints seem to support the result of the primary endpoint since a positive trend is seen for all of them:

- LCI5.0: the change from baseline was -0.28. It is consistent and reassuring although the effect is small.

- ppFEV1: the change form baseline was +2.7. Again the size effect is small compared to that seen in other studies in which IVA was given to CF patients with different mutations.

- Sweat chloride: a reduction of 9.2 mmol/L (-12.4, -5.9) was seen. The effect size is limited compared to the effect of Kalydeco on sweat chloride in other mutations. The waterfall plot shows that almost all patients on IVA had a reduction in sweat chloride levels. For some of them the reduction versus placebo was higher than 10 mmol/L.

- An important increase in CFQ-R respiratory is reported (+18.7). This improvement is impressive and somehow unexpected considering the limited size effect on other clinical endpoints and relevant parameters as well as the short duration of the study.

- organoids: Overall organoids for both mutations showed swelling in the FIS assay. No correlation could be demonstrated between the degree of swelling and the response in clinical endpoints.

Based on the present data it is not possible to know if ivacaftor has any beneficial effect in the CF paediatric population with a 3849 + 10KB C→T or D1152H-CFTR mutation since all data have been provided for the overall population. As these results have been submitted under the Article 46 of the paediatric regulation the MAH has been asked to provide the results of the primary and additional endpoints for the patients between 12 and less than 18 years of age provided that they represent a substantial fraction of the whole population (more than 50%) even when due to the small number the value is expected to be mainly descriptive. According to the MAH, only 8 subjects were younger than 18 years of age (21% of the study population). Given the small numbers, the MAH has not provided any data for this particular subset what it is considered acceptable.

Safety results

Mean exposure duration was similar for placebo (8.2 weeks) and ivacaftor (8.1 weeks) groups.

Only TEAEs are shown in this application. In both placebo and ivacaftor groups 57.9 % of patients had at least one TEAE. Most of them were considered not related and only 2 patients on placebo (5.3%) and 7 on ivacaftor (18.4%) had a severe AE.

The most frequent TEAEs were infections and infestations, in particular of the respiratory tract that it is expected in this CF population, followed by respiratory, thoracic and mediastinal disorders. No patients had increases in transaminases above 8 x ULN. The incidence of ALT or AST levels >3 to ≤ 5 x ULN was 2.6% in patients on placebo versus 0% in subjects on kalydeco. A patient on IVA had elevations of bilirrubin >1.5 to ≤ 2 x ULN. The percentage of patients with >ULN to 1.5 x ULN was higher in patients receiving kalydeco (7.9% versus 5.4%, respectively).

Mild hepatic transaminase elevation is a common occurrence in CF patients particularly among young children with cystic fibrosis. Elevated transaminases have been also reported in patients with CF receiving ivacaftor. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin. A warning on the increase of transaminasases in CF patients treated with ivacaftor is in section 4.4 of the SmPC.

3. CHMP overall conclusion and recommendation

Study 127 has been submitted under Article 46 of Paediatric Regulation that requires MAH to submit information on studies conducted in children of authorised medicines that have been completed since the Paediatric Regulation came into force in 2007.

Such study included subjects older than 6 whose mean age was 32 years and there were patients as old as 64 years old. The MAH has provided the results for the whole population, comprising children adolescents and adults. Overall, efficacy data from study 127 showed a positive trend in all parameters assessed although the effect size is limited. No new safety data have been identified in the study either. However, no specific information has been provided for subjects younger than 18 years of age.

The sample size of study 127 was very small (n=38) so the number of patients younger than 18 years included was expected to be also very limited. As the main aim interest of Art P46 of the "Paediatric

Regulation" is to get efficacy and safety data from a paediatric perspective the MAH was requested to provide the baseline characteristics and the results for the primary and additional endpoints as well as the safety data for the paediatric population (children plus adolescents) in case that the paediatric population represented at least 50% of the whole population. According to the MAH, the percentage of children and adolescents was only 21% (8/38) of the study population. Given the small numbers, no sound conclusions can be drawn from the efficacy and safety perspective.

The benefit/risk balance of Kalydeco remains positive. No changes to the SmPC are considered necessary.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Fifty subjects were initially planned to participate in the study but instead, 38 have been randomized. The MAH should explain numerically how this reduction of the planned sample size affects to the precision calculated and to the results presented.
2. Only 4 subjects were younger than 12 years of age in study 127 and it is unknown how many of them were adolescents (between 12 and less than 18 years of age). However, for the purpose of this submission (Art 46 of the "Paediatric Regulation") it is of interest to have information the paediatric population. As the sample size is very limited (38 subjects including children, adolescents and adults) the MAH is requested to provide the following data <u>if the number of children and adolescents represent a substantial proportion of the whole population (i.e., 50% or more)</u>:

    - their baseline characteristics: ppFEV1 (including categories <40; ≥40 and <70; ≥70 and ≤90; and >90); sweat chloride, LCi2.5, LCI5 and CFQR at baseline, and the genotype of each of them. For all this parameters, the mean (SD), median, minimum and maximum values should be provided.

    - as there were sweat chloride values as low as 12 mmol/L were reported in study 127 (not likely indicative of CF) the MAH should provide the individual values for the paediatric patients with sweat chloride values under 60 mmol/L and the corresponding mutation.

    - the results for the primary and additional endpoints: change from baseline in LCI, in ppFEV1, in sweat chloride, in CFQ-R, and the effect on organoids.

5. Assessment of the MAH responses to the Request for Supplementary Information

Question 1

Fifty subjects were initially planned to participate in the study but instead, 38 have been randomized. The MAH should explain numerically how this reduction of the planned sample size affects to the precision calculated and to the results presented.

<u>MAH's position</u>

With 38 randomized subjects, the posterior probability that the average treatment difference (IVA-Placebo) through 8 weeks exceeds 0 for the primary endpoint of lung clearance index (LCI2.5) is 0.24%, and the half-width of the 95% confidence interval (CI) from the mixed-effects model for repeated measures (MMRM) for the primary endpoint is 0.45. If 50 subjects were randomized as planned in a 1:1 ratio to the 2 crossover sequences, this posterior probability would be further reduced. In addition, the half-width of the 95% CI would be reduced to 0.40. The conclusion however remains the same.

CHMP comment

The MAH has provided data to justify that the precision is still relevant even when they have enrolled 38 patients instead of the 50 patients planned. It is agreeable that the conclusion remains the same. It should be noted that the number of paediatric patients enrolled in this study represents only the 21% of the study population. Please see Question 2 for more details.

Question 2

Only 4 subjects were younger than 12 years of age in study 127 and it is unknown how many of them were adolescents (between 12 and less than 18 years of age). However, for the purpose of this submission (Art 46 of the "Paediatric Regulation") it is of interest to have information the paediatric population. As the sample size is very limited (38 subjects including children, adolescents and adults) the MAH is requested to provide the following data if the number of children and adolescents represent a substantial proportion of the whole population (i.e., 50% or more):

- their baseline characteristics: ppFEV1 (including categories <40; ≥40 and <70; ≥70 and ≤90; and >90); sweat chloride, LCI2.5, LCI5 and CFQ-R at baseline, and the genotype of each of them. For all these parameters, the mean (SD), median, minimum and maximum values should be provided.

- as there were sweat chloride values as low as 12 mmol/L were reported in study 127 (not likely indicative of CF) the MAH should provide the individual values for the paediatric patients with sweat chloride values under 60 mmol/L and the corresponding mutation.

- the results for the primary and additional endpoints: change from baseline in LCI, in ppFEV1, in sweat chloride, in CFQ-R, and the effect on organoids.

MAH's position

There were 4 children <12 years of age and 4 adolescents 12 to <18 years of age in the study population of 38 subjects. The percentage of children and adolescents is 21% (8/38) of the study population, which is less than 50%. Due to the number of children and adolescents being such a small percentage of the population and not reaching a substantial proportion of the whole population no further study data are presented for these subjects.

CHMP comments

The sample size of study 127 was very small (n=38) so the number of patients younger than 18 years included was expected to be also very limited. As the main aim interest of Art P46 of the "Paediatric Regulation" is to get efficacy and safety data from a paediatric perspective the MAH was requested to provide the baseline characteristics and the results for the primary and additional endpoints as well as the safety data for the paediatric population (children plus adolescents) in case that the paediatric population represented at least 50% of the whole population. According to the MAH, the percentage of children and adolescents was only 21% (8/38) of the study population. Given the small numbers, no sound conclusions can be drawn from the efficacy and safety perspective.

The benefit/risk balance of Kalydeco remains positive. No changes to the SmPC are considered necessary.