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Early View

Original article

An innovative Phase II trial to establish proof of efficacy and optimal dose of a new inhaled ENaC inhibitor BI 1265162 in adults and adolescents with cystic fibrosis (BALANCE-CF™ 1)

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An innovative Phase II trial to establish proof of efficacy and optimal dose of a new inhaled ENaC inhibitor BI 1265162 in adults and adolescents with cystic fibrosis (BALANCE-CF™ 1)

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Abstract

Inhibition of the epithelial sodium channel (ENaC) represents an important, mutation-agnostic therapeutic approach to restore airway surface liquid in patients with cystic fibrosis (CF). A Phase II trial of the ENaC inhibitor BI 1265162, inhaled via the Respimat® Soft Mist™ inhaler, in patients aged ≥12 years with CF is being conducted to assess the efficacy and safety of BI 1265162, on top of standard CF treatment (NCT04059094).

BALANCE-CF™ 1 is a multinational, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging trial consisting of 2 weeks' screening, 4 weeks' randomised treatment and 1 week follow-up. Ninety-eight patients, including ≥21 adolescents, will be randomised. First, 28 patients will be allocated to the highest dose of BI 1265162 (200 µg twice daily [BID]) or placebo in a 1:1 ratio. The remaining 70 patients will be allocated to one of five treatment arms (200 µg, 100 µg, 50 µg, 20 µg or placebo BID), with a final distribution ratio of 2:1:1:1:2. Recruitment and randomisation will begin with adult patients. An independent Data Monitoring Committee will review safety data to advise on inclusion of adolescents and study continuation. A futility analysis will be conducted after 28 patients to prevent exposure of further patients in case of insufficient evidence of clinical efficacy. The design ensures that potential for effect is assessed ahead of wider enrolment, allowing investigation of a dose-response effect with minimal patient numbers.

The results will increase understanding of efficacy, safety and optimal dosing of the inhaled ENaC inhibitor BI 1265162 in adults and adolescents with CF.

Lay summary

An ENaC inhibitor is a type of treatment that may keep the surface of the airways hydrated and improve mucus properties. This may make it easier for patients with cystic fibrosis (CF) to cough and keep their airways clear. Here, we describe the design of a trial (BALANCE-CF™ 1) that will look at whether the ENaC inhibitor, BI 1265162, at different doses improves respiratory function and whether it is safe and well tolerated in patients with CF. The drug is delivered by the Respimat® Soft Mist™ inhaler, a device that helps the medication to reach deep into the lungs. The trial will include 98 adults and adolescents. Adolescents can only enter the trial once a committee independent of the researchers has reviewed the safety results from adults in the trial. Once the first 28 patients finish 4 weeks of treatment with either BI 1265162 or placebo, the researchers will assess how well BI 1265162 works to improve respiratory function, to make sure that the other patients in the trial do not continue taking the medicine in case it might not be effective.

Take home message (256/256 characters):

BALANCE-CF™ 1 is an innovative Ph II trial in patients aged ≥12 years with CF to assess the efficacy and safety of the inhaled ENaC inhibitor BI 1265162 vs placebo. The results will increase understanding and support further investigation in Ph III trials

Introduction

Cystic fibrosis (CF) is a life-threatening, autosomal recessive genetic disease caused by mutations in the CF Transmembrane Conductance Regulator (*CFTR*) gene, which encodes an ion channel protein [1, 2]. The CFTR protein mediates the transport of chloride and other anions across the apical membrane of epithelial cells. Defective or absent CFTR protein in the airway epithelial cells leads to reduced chloride and bicarbonate excretion and thus reduced mucus hydration in the airways [2-4].

Loss of function of CFTR is further affected by the epithelial sodium channel (ENaC) protein, which is influenced by CFTR [5]. The nature of the interaction between CFTR and ENaC modulation is not fully understood, but it is known that in CF, ENaC activity is hyperactivated when CFTR function is reduced or absent [2, 5, 6]. Upregulation of ENaC activity leads to increased absorption of sodium ions and water from the luminal surface into the epithelial cell, causing reduced airway surface liquid (ASL) volume and dehydrated mucus. This results in poor mucociliary clearance (MCC) [2, 6] and promotes bacterial colonisation, infection, lung inflammation and airway obstruction [7].

CFTR modulator therapies have become available that target specific dysfunctional CFTR proteins. Combinations of modulators extend the number of eligible mutations. Despite the approval of CFTR modulator therapies, there is still a need for symptomatic treatment to reduce the risk of CF-related exacerbations, improve individual quality of life, and prolong patient survival [27]. This applies both for patients eligible to take a CFTR modulator and for patients who do not take this class of medication. ENaC inhibition, a mutation-agnostic approach, has the potential to restore ASL hydration and enhance MCC [28]. Treatments that target ENaC in the presence of CFTR modulators could have a synergistic electrophysiological effect helping to normalise ASL volume and MCC [2]. ENaC inhibition (aimed at reducing cation absorption) could provide an enhanced electrical drive increasing CFTR anion secretion [2]. Thus, ENaC inhibition could potentially enhance the effect of CFTR modulation, thereby further improving CFTR function [2, 10].

A number of ENaC inhibitors have been tested both preclinically and clinically in patients with CF. These preclinical and clinical studies showed positive initial results, followed by non-significant results in later clinical studies. Reasons for discontinuation of development included adverse events related to systemic hyperkalaemia, unfavourable pharmacokinetics (PK) and pharmacodynamics, weak affinity for the channel and short duration of action [2].

BI 1265162 is a novel ENaC inhibitor, inhaled via the Respimat® Soft Mist™ inhaler. This device was chosen due to its high efficiency in drug delivery and high lung deposition, as well as ease of use for patients. It has already been successfully deployed in therapeutics for chronic obstructive pulmonary disease and asthma [12], and has been previously used in studies with tiotropium in patients with CF [13].

Preclinical analysis demonstrated that BI 1265162 effectively inhibits sodium ion absorption, leading to a reduction in water resorption in human and murine cell lines, and liquid absorption in a rat lung model, and accelerates MCC in a sheep model without any relevant changes in plasma electrolyte concentrations [16-18]. BI 1265162 has a 30–70-fold higher potency compared with the prototypical ENaC inhibitor, amiloride, in preclinical studies [16]. In normal and CF human airway epithelia models, BI 1265162 decreased water transport and increased MCC, alone and in combination with

CFTR modulators (ivacaftor/lumacaftor [IVA/LUM]), with BI 1265162 increasing the effects of IVA/LUM in CF epithelium to reach the effect size seen in healthy epithelium with IVA/LUM alone, supporting a possible synergistic effect of BI 1265162 with CFTR modulators [19, 20].

Phase I studies with healthy volunteers who received doses of up to 1,200 µg per day support that BI 1265162 was safe and well tolerated in a single-dose trial (NCT03349723) and multiple-dose trial (NCT03576144) over a 1-week period [21]. Renal excretion was a very minor elimination route for the unchanged parent compound [22].

Based on promising preclinical and Phase I results, BI 1265162 is now in Phase II development. BALANCE-CF™ 1 is a 4-week, dose-ranging, double-blind, parallel-group, Phase II trial in patients aged 12 years and above with CF. The trial is being conducted to assess the efficacy and safety of four dose levels of BI 1265162 versus placebo, on top of standard CF treatment (NCT04059094). Here, we present and discuss the trial methodology.

Research methods

Objectives

The primary objective of BALANCE-CF™ 1 is to assess the efficacy and safety of four doses of twice-daily (BID) BI 1265162 (20 µg, 50 µg, 100 µg and 200 µg), inhaled via the Respimat® Soft Mist™, inhaler compared with placebo on top of standard CF therapies, including CFTR modulators, in patients aged 12 years and above with CF. Pharmacokinetics (PK) will also be assessed.

Study design

BALANCE-CF™ 1 is a multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging trial, consisting of a 2-week screening period, a 4-week randomised treatment period and a 1-week follow-up period (Figure 1). A total of 98 patients, including at least 21 adolescents, will be randomised. First, 28 patients will be allocated to the highest dose of BI 1265162 (200 µg BID) or placebo in a 1:1 ratio. Once the first 28 patients are randomised, the remaining 70 patients will be allocated to one of five treatment arms (200 µg BID, 100 µg BID, 50 µg BID, 20 µg BID or placebo BID) in an equal ratio.

Approximately 50 investigational sites in nine countries in Europe and North America are involved. Recruitment and randomisation will begin with adult patients only. Enrolment of adolescent patients will be based on periodic reviews of adult patient safety data after every 7 patients have completed the trial treatment period, performed by an independent Data Monitoring Committee (DMC; in collaboration with the Cystic Fibrosis Foundation). The DMC will advise on continuation of the study and the initiation of enrolment of adolescent patients. Once the DMC has permitted enrolment of adolescent patients, the periodic safety reviews will occur every 3 months.

An interim futility analysis will be conducted on the primary efficacy endpoint once the first 28 patients have completed the 4-week treatment period to prevent exposure of further patients in case of insufficient evidence of clinical efficacy. For the primary endpoint, insufficient evidence of clinical efficacy is defined, for example, as an improvement in per cent predicted trough forced

expiratory volume in 1 second (FEV_1) of less than 1.5%. The effect of single patients; point estimates, confidence intervals and variance; stability of the treatment effect; baseline comparability; and other potentially important factors may be considered.

If the independent DMC has permitted inclusion of adolescents by this time, the interim futility analysis may also include adolescent data. Recruitment will continue during preparation and conduct of the interim analysis.

Due to its mutation-agnostic treatment approach, which allows for combination with all other standard-of-care CF drugs including CFTR modulators, BI 1265162 will be assessed as add-on therapy to standard of care as the same effect size is assumed and is to be assessed in predefined subgroup analyses at the final trial evaluation. Therefore, patients will remain on their current treatment (including CFTR modulator therapy) as long as their therapy is stable (periodic or continuous) and has been established for at least 4 weeks before randomisation. For patients who are receiving a stable regimen of inhaled cycling antibiotics, Visit 2 (first treatment day) should occur on Day 1 of an "On-cycle" (±1 or 2 days), regardless of the antibiotic. For patients cycling different inhaled antibiotics, Visit 2 should occur on Day 1 of a new antibiotic cycle. To reduce short-term impact on lung function, a standardised washout of bronchodilators prior to spirometry is required. LCI will also be assessed using a standardised washout recording system. Standardisation of physiotherapy is required at visit days, *i.e.* to be performed in the same fashion as at screening. Detailed subgroup analysis will be planned for the final analysis.

The protocol for BALANCE-CF™ 1 was reviewed by the Cystic Fibrosis Foundation Therapeutics Development Network and the European Cystic Fibrosis Society – Clinical Trials Network and approved by competent authorities and Institutional Review Board/Independent Ethics Committee of the respective investigational sites.

Endpoints

The primary endpoint of BALANCE-CF™ 1 is change from baseline in per cent predicted trough (within 30 minutes prior to dosing) FEV_1 after 4 weeks of treatment. The primary endpoint will be assessed in the first 28 patients in the interim futility analysis, and evaluated further in all 98 patients at study completion. FEV_1 was selected as the primary endpoint as it correlates with clinical status and mortality in CF and it is expected that improved mucus clearance associated with BI 1265162 would improve FEV_1. In addition, the study includes a wide range of patients (FEV_1 40–90%), a population for which endpoints such as LCI might be more difficult to assess at the lower range of the FEV_1 spectrum.

Secondary efficacy, safety and PK endpoints are described in Table 1

Recruitment and sample size calculation

Patients will be screened from approximately 50 trial sites to ensure randomisation of at least 98 patients including at least 21 adolescents. Screening of patients is competitive, with screening at trial

sites stopping once a sufficient number of patients have been screened. It is expected that 2–3 patients will be randomised at each trial site.

In order to ensure 12 evaluable patients per arm with primary endpoint data for interim analysis, at least 14 patients per arm will be randomised (total 28). In order to ensure an additional 12 patients per group are evaluable for final analysis, at least 14 patients will be randomised per treatment group (total 70). Overall, 98 patients will be randomised in the trial. This guarantees an overall power of at least 80% for all true candidate monotone shapes; and overall type I error is also controlled below 5%. Pre-specified candidate models and assumptions for treatment effect size and standard deviation will be required for performing the Multiple Comparison Procedures – Modelling (MCP-Mod) analysis. This calculation has been performed using R software, version 3.2.2.

Inclusion and exclusion criteria

Males or females with CF aged ≥12 years at screening were included in BALANCE-CF™ 1. Further inclusion and exclusion criteria are detailed in Table 2.

Randomisation of patients

Prior to patient participation in BALANCE-CF™ 1, written informed consent will be obtained from each patient (or the patient's legally accepted representative) according to International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines and to the regulatory and legal requirements of the participating country.

Twenty-eight adult patients – or adolescent patients, if permitted by the DMC – will be randomised to receive either the highest dose (200 µg BID) or placebo. An interim futility analysis will be conducted by the study sponsor, independent of the trial team, to assess whether the drug has the potential to show efficacy in order to prevent further enrolment in the case of insufficient clinical potential. Patients, investigators and all those involved in trial conduct or analysis will remain blinded with regard to the randomised treatment assignments until after database unlock.

Recruitment will continue during conduct of the interim analysis. After randomisation of the first 28 patients, the remaining 70 patients will be randomised to all study arms in an equal allocation for this second portion of the study, leading to a final distribution ratio of 2:1:1:1:2 to receive BID placebo, 20 µg, 50 µg, 100 µg or 200 µg BI 1265162 via the Respimat® Soft Mist™ inhaler (Figure 1). This unbalanced design follows the MCP-mod approach [25] and ensures that a dose-response signal is established using multiple comparison procedures before the dose-response curve and target doses of interest are subsequently estimated using modelling techniques. The doses were selected in order to cover the expected therapeutic range (50–200 µg) and a sub-therapeutic dose (20 µg), which is required for modelling of the dose-response shape.

Randomisation will be stratified by age (12–17 years and ≥18 years) to ensure that adolescent patients are equally randomised to each treatment group as per the final distribution ratio (≥6 adolescents in both the placebo and 200 µg BI 1265162 BID group, and ≥3 adolescents in each of the 20 µg, 50 µg and 100 µg BI 1265162 BID groups).

It is anticipated that this study will complete enrolment by Quarter 2/3 of 2020.

Outcome assessments

Efficacy will be assessed using measures of pulmonary function (FEV_1 and forced vital capacity evaluated using Global Lung Initiative lung function reference equations [26]), LCI (by nitrogen multiple breath washout test), and questionnaires on health-related quality of life (CFQ-R) and symptoms (CASA-Q).

Safety will be monitored throughout the trial by AE reporting, safety laboratory tests, vital signs measurements, 12-lead electrocardiogram and periodic safety data reviews by the DMC. Discontinuation criteria in case of confirmed increased levels of serum potassium are implemented.

PK analysis will be performed in blood using a sparse population PK approach that jointly analyses the combined data from this study along with those from the Phase I study in healthy volunteers.

Planned analyses and assessments

The analyses for proof of concept and dose-finding will be performed using multiple comparison and modelling techniques, whereby several possible dose-response models will be evaluated.

To assess the change from baseline in FEV_1 per cent predicted at 4 weeks of treatment, a restricted maximum likelihood-based approach using a mixed model with repeated measurements will be carried out. The analysis will include the fixed, categorical effects of treatment at each visit, age (adolescents vs. adults) and the fixed continuous effects of baseline at each visit. “Visit” will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The linear mixed-effects model will also be used to analyse the secondary endpoints, with resulting confidence intervals and p-values considered as nominal or descriptive.

Patients should remain on their usual stable therapy throughout the study. However, if patients change other CF treatments during the trial period, these subgroups of patients will be investigated and descriptive analyses will be conducted. In addition, the impact of baseline characteristics, including lung function FEV_1 categories and CF gene status, will be considered as possible subgroups.

Ethical approval

The trial was initiated after review and approval by the respective Institutional Review Board/Independent Ethics Committee and competent authority according to national and international regulations.

Funding of study

This study (BALANCE-CF™ 1) is funded by Boehringer Ingelheim.

Discussion

Following promising preclinical and Phase I results, the results of the Phase II clinical trial, BALANCE-CF™ 1, will increase understanding of safety, efficacy and optimal dosing of the new inhaled ENaC inhibitor BI 1265162 in adults and adolescents with CF.

Despite the approval of CFTR modulator therapies, there is still a need for a mutation-agnostic therapy that operates independently of CFTR function and mutation to benefit all patients with CF [2]. In murine models over-expressing ENaC with resultant CF-like disease characteristics, including mucus plugging and impaired MCC, ENaC inhibition with amiloride resulted in significant therapeutic benefits [29]. Also, in patients with CF homozygous for F508del, rare loss-of-function mutations in genes encoding the ENaC may be associated with a long-term, non-progressive phenotype, further supporting the potential of ENaC inhibition [30].

The ENaC inhibitor BI 1265162 has higher preclinical potency than previously studied ENaC inhibitors [16, 17, 19]. A number of previous ENaC inhibitors have failed in clinical development. The HOPE-1 Phase II trial of SPX-101, a peptide analogue that promotes ENaC channel internalisation [4], showed no effect of SPX-101 on FEV_1 per cent predicted in the full data set, despite promising interim Phase II data and despite Phase I and preclinical experiments demonstrating positive results [4, 7, 31]. The HOPE-1 trial has now been discontinued [32]. Unlike HOPE-1, BALANCE-CF™ 1 assesses not only FEV_1 per cent predicted, but also change from baseline in LCI. Compared with FEV_1, LCI reflects ventilation inhomogeneity and disease effects in the peripheral airways – effects which may occur earlier in the disease process and are not detected with spirometric measures such as FEV_1 [33]. This Phase II trial builds upon the robust preclinical evidence of BI 1265162, together with safety data derived from a single-rising dose and a multiple-rising dose Phase I trial [21].

Preclinical animal model data demonstrate that BI 1265162 reduces liquid absorption in rat lungs and increases MCC in sheep, without any systemic effects [16, 18]. In addition, inhibition of ENaC was maintained for 5 days, as indicated by attenuation of water transport in normal and CF airway epithelia *in vitro* [20]. In clinical Phase I trials in which healthy volunteers were given inhaled total daily doses of up to 1200 µg, BI 1265162 was well tolerated, and renal excretion was a very minor elimination route for the unchanged parent compound. Further evaluation of the absorption, distribution, metabolism and excretion of BI 1265162 is ongoing. These data demonstrate a good safety profile for the ENaC inhibitor BI 1265162, supporting the present study design where the first patients are allocated to the highest dose of BI 1265162 (200 µg BID).

The study design of BALANCE-CF™ 1 has several advantages. The unbalanced design, which follows the MCP-mod approach [25], allows assessment of efficacy and dose ranging with minimal patient numbers. By first including patients in the highest dose *versus* placebo with an interim futility analysis, patient exposure is minimised should there be little probability that efficacy can ultimately be detected. This also facilitates minimal exposure to potentially ineffective lesser doses. Moreover, adolescents are enrolled into the study based on periodic DMC review of safety data (every 7 participants who have been enrolled and exposed to 4 weeks of treatment). By including

adolescents in this study, a bridge of the PK and efficacy to adults can be made to allow a rational Phase III study design that includes adolescents and adults.

Another strength of the study is that BI 1265162 is taken on top of standard of care, including CFTR modulator therapy (provided the medication regimen for CF has been stable for at least 4 weeks prior to randomisation). BI 1265162 is believed to work on top of other CF medication, independently of mutation status, as demonstrated in *in vitro* studies where BI 1265162 decreased water transport and increased MCC, with BI 1265162 increasing the effects of the CFTR modulators IVA/LUM on CF epithelium to reach the effect size seen in healthy human epithelium with IVA/LUM alone [19, 20]. CFTR modulators may only restore approximately 20–50% of CFTR function [10]; therefore, BI 1265162 could potentially further improve CFTR function. The study design on top of standard care may result in further heterogeneity of patients. However, the potential effects of variability based on underlying therapy being introduced should be minimised by the requirements that standard of care treatments remain stable for at least 4 weeks prior to and during the trial, and that changes relative to baseline will be assessed. In addition, effect size is to be assessed in predefined subgroup analyses at the final trial evaluation.

Conclusion

BALANCE-CF™ 1 includes an innovative trial design, where patients are first randomised to receive the highest dose of BI 1265162 or placebo before an interim futility analysis is performed, which prevents exposure in case of insufficient ability to detect clinical efficacy. An unbalanced MCP-Mod design ensures that a dose-response signal can be investigated whilst requiring minimal patient numbers. Adolescents will only be enrolled once safety data from adults are reviewed and adolescents' inclusion recommended by an independent DMC. BALANCE-CF™ 1 includes both FEV_1 and LCI, which assess different aspects of airway physiology, as efficacy endpoints.

The results of BALANCE-CF™ 1 will increase understanding of safety, efficacy and optimal dosing of the new inhaled ENaC inhibitor BI 1265162 in adults and adolescents with CF. If efficacy and safety are demonstrated, the results will support further investigation of BI 1265162 in Phase III trials.

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Table 1. Secondary efficacy, safety and PK endpoints

Efficacy	Safety	PK
Change from baseline in LCI for patients with FEV_1 >60% of predicted values at screening after 4 weeks of treatment	Percentage of patients with treatment-emergent AEs up to Day 36	Concentration of the analyte in plasma at time t following dose N ($C_{t.N}$)
Change from baseline in CFQ-R after 4 weeks of treatment	–	Pre-dose concentration measured for dose N ($C_{pre.N}$)
Change from baseline in CASA-Q after 4 weeks of treatment	–	Area under the concentration–time curve of the analyte in plasma until t hours after dose N ($AUC_{0-t,N}$)

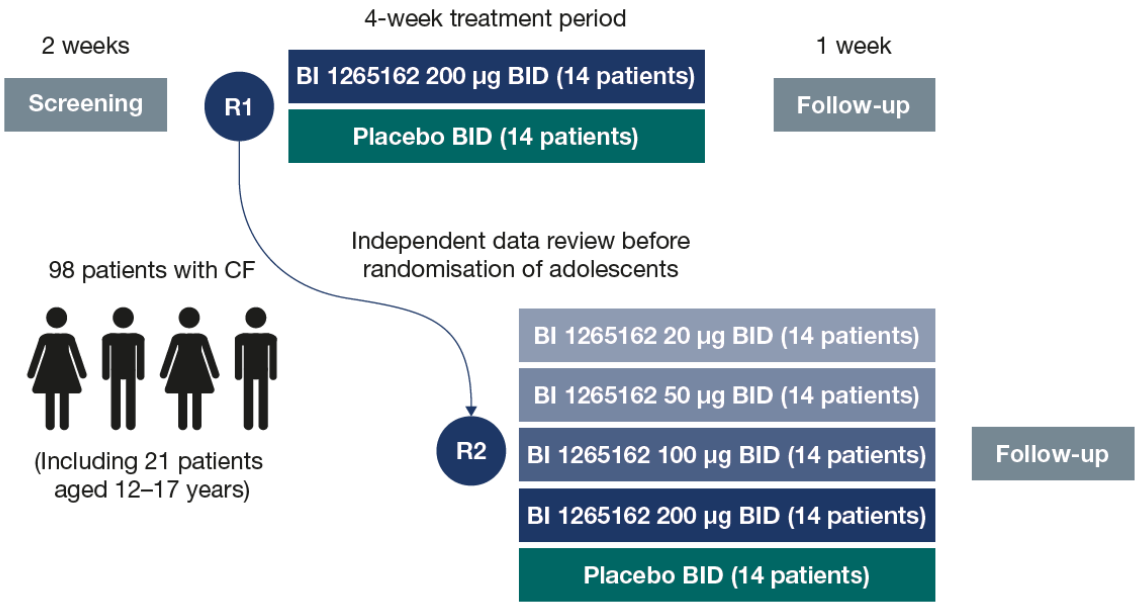
AE, adverse event; CASA-Q, Cough and Sputum Assessment Questionnaire; CFQ-R, CF Questionnaire – Revised; FEV_1, forced expiratory volume in 1 second; LCI, lung clearance index; PK, pharmacokinetics.

Table 2. Inclusion and exclusion criteria for study participants

Inclusion criteria	Exclusion criteria
Male or female, aged ≥12 years at screening	Acute upper or lower respiratory tract infection ≤4 weeks prior to randomisation
Diagnosis of CF (positive sweat chloride ≥60 mEq/L, or genotype with two identifiable mutations and ≥1 clinical phenotypic feature of CF)	Pulmonary exacerbation requiring the use of antibiotics or oral corticosteroids ≤4 weeks prior to randomisation
FEV_1 (according to Global Lung Initiative) ≥40 and ≤90% predicted at screening and pre-dose at Visit 2	

CF, cystic fibrosis; FEV_1, forced expiratory volume in 1 second.

Figure 1. Trial design



BID, twice daily; CF, cystic fibrosis; R, randomisation.