Efficacy and safety of inhaled ENaC inhibitor BI 1265162 in patients with cystic fibrosis: BALANCE–CF™ 1 – a randomised, Phase II study

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Online supporting information

Methods

Objectives

The objectives of this study were to assess the efficacy, safety and pharmacokinetics of twice-daily (BID) doses of 20 µg, 50 µg, 100 µg and 200 µg BI 1265162, inhaled using the Respimat® Soft Mist™ inhaler (SMI), in addition to standard cystic fibrosis (CF) therapies, including cystic fibrosis transmembrane conductance regulator (CFTR) modulators, compared with BID placebo, in patients aged ≥12 years old.

Study design

This study was a multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study carried out at 29 sites (26 sites with screened patients) across eight countries [1]. A total of 74 patients were screened (enrolled) by 26 centres in Belgium (2 sites), Canada (2 sites), France (5 sites), Germany (5 sites), Spain (1 site), Sweden (2 sites), the United Kingdom (1 site) and the United States (8 sites). The trial was carried out from 24 September 2019 to 24 April 2020.

The patient population in this study was exclusively male. Because this was the first Phase II study performed with this molecule and embryo-foetal development data were not available at study start, Women of Childbearing Potential (WoCBP) were excluded in the initial protocol. Availability of embryo-foetal development data then allowed inclusion of WoCBP using adequate contraception. This was reflected in a

revision of the clinical trial protocol on 18 November 2019, which needed to undergo local regulatory approval processes before implementation.

The study consisted of a 2-week screening period, a 4-week randomised treatment period and a 7-day follow-up period (Figure 1). As the investigational drug was assessed as an add-on therapy to standard of care, patients remained on a stable CF medication regimen (with the exception of bronchodilators, which were withheld prior to lung function testing) from 4 weeks prior to randomisation until the end of the treatment period. Concomitant use of CFTR modulators was allowed, if stable.

A stable medication regimen is defined as the current medication regimen for CF that the patient has been following for at least 4 weeks before Day 1 (randomisation).

A total of 98 patients, starting with adults with the possibility to extend to also include adolescents (from 12 years of age), were planned for randomisation. Twenty-eight patients were first allocated to the highest dose of BI 1265162 (200 µg BID) or placebo BID in a 1:1 ratio (n=14 per group). Once the first 28 patients were randomised, the remaining 70 patients were to be allocated to one of the five treatment arms (200 µg, 100 µg, 50 µg, 20 µg or placebo BID) in a 1:1:1:1:1 ratio, to result in a final ratio of 2:1:1:1:2.

The sample size calculation was based on the following assumptions:

- the primary endpoint (i.e. change from baseline in percent predicted trough forced expiratory volume in 1 second [ppFEV$_1$] at Week 4) was normally distributed
- sided significance level $\alpha = 5\%$
- mean treatment difference (for the highest dose of BI 1265162 vs placebo) was 6% (for interim futility analysis only)

- true maximum treatment effect size of BI 1265162 versus placebo was 6%
- standard deviation was 8% [2]
- pre-specified candidate models.

Randomisation to treatment groups was performed by ALMAC Clinical Technologies Services, United States using an Interactive Voice/Web Response System (IXRS), assigning the appropriated medication number based on the treatment sequence. The randomisation code was generated using a validated system and verified by a trial-independent statistician. The randomisation scheme was provided by Boehringer Ingelheim. A block size of 4 was used for the first 28 adult patients. For the remaining adult patients, a block size of 13 was used. For adolescents, a block size of 7 was to be used.

Patients, investigators, and everyone involved in trial conduct or analysis were to remain blinded with regard to the randomised treatment assignments until after database lock. All treatments were inhaled via the Respimat® SMI. Medications were dispensed by the investigator, study coordinator or pharmacist, depending on the site structure.

The start of adolescent patients' enrolment was to be based on review of adult safety data, carried out by an independent data monitoring committee (DMC) in collaboration with the Cystic Fibrosis Foundation, after every seven patients had completed the treatment period.

An interim futility analysis was planned to be conducted on the first 28 patients to assess efficacy and to prevent exposure of further patients in case of insufficient efficacy. Per protocol, recruitment was to continue during preparation and conduct of

the interim analysis. A decision on discontinuation at the interim analysis was to be made using the following stopping rule:

> Increase in trough percent predicted forced expiratory volume in 1 second ($ppFEV_1$) % <1.5% AND decrease (improvement) in lung clearance index (LCI) <0.3 units.

These criteria were based on the opinion that a clinically meaningful improvement in $ppFEV_1$ or LCI would not be realistically expected to reach an effect considered clinically meaningful should the study fully recruit, i.e. a futility analysis.

Key inclusion and exclusion criteria

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

- Women of childbearing potential on inadequate contraception (subject to protocol amendment).
- Starting a new chronic medication for CF within 4 weeks of randomisation.

Endpoints

The primary endpoint was the change from baseline in trough (30 minutes prior to dosing) ppFEV$_1$ after 4 weeks of treatment.

Secondary endpoints were:

- Change from baseline in LCI as assessed by N_2 multiple breath washout (N_2MBW) test after 4 weeks of treatment (patients qualified for N_2MBW test if they had a FEV$_1$ >60% of predicted values at screening and were able to complete the N_2MBW test at Visit 2).
- Change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) [3] total score after 4 weeks of treatment.
- Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q©) after 4 weeks of treatment [4].
- Percentage of patients with treatment-emergent adverse events (AEs) up to Day 36, clinical laboratory assessments, vital signs, electrocardiograms, physical examination and chest examination.
- Maximum measured concentration of the analyte in plasma following dose N up to Day 36.
- Pre-dose concentration measured for dose N up to Day 29.

- Area under the concentration−time curve of the analyte in plasma until t hours after dose N up to Day 36.

Treatment compliance

The extent of patient compliance (percentage of prescribed Respimat actuations taken) was measured by the use of a diary, dispensed to patients at Visit 2, with compliance checks and checks of diaries at Visits 3 and 4. A compliance of 80–120% was required.

Statistical analyses

The planned analyses for proof of concept and dose-finding were to use multiple comparison and modelling techniques to measure the difference between the placebo and BI 1265162 treatment groups. Due to a halt in recruitment because of the COVID-19 pandemic followed by discontinuation based on the interim futility results, sample size was limited for the final analysis. Power calculations for the final analysis were based on having $ppFEV_1$ results for at least 24 evaluable patients each for the BI 1265162 200 µg and placebo BID treatment groups and at least 12 evaluable patients each for all other treatment groups; however, the treated set after study termination, which was used for analysis of the primary endpoint, included only 18 patients each in the BI 200 µg and placebo treatment groups and 5 or 6 patients each in the other treatment groups.

To assess the change from baseline in trough $ppFEV_1$ after 4 weeks of treatment, a restricted maximum likelihood-based approach using a mixed model with repeated

measurements (MMRM) was carried out. The analysis included the fixed, categorical effects of treatment at each visit (baseline, Week 1, Week 4), age and the fixed continuous effects of baseline at each visit. Visits were treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

Change from baseline in LCI after 4 weeks of treatment was analysed by covariance (ANCOVA), with adjustment for categorical effects of treatment and the fixed continuous effect of baseline. CASA-Q® analysis was descriptive in nature, with scores described by treatment and domain score for baseline, Day 8, Day 29 and change from baseline. CFQ-R analysis was also descriptive in nature, with total and domain scores for baseline, Day 29 and change from baseline described separately for each treatment group.

Sensitivity analyses

Sensitivity analyses were pre-specified and permitted by the study statistical analysis plan to address any outlier data points and expected variability. Data were reviewed by an Interim Analysis Assessment Committee (Boehringer Ingelheim, independent from the study team) at the interim futility analysis for the impact of outliers.

Three sensitivity analyses were carried out for both $ppFEV_1$ and LCI endpoints. In the first analysis, the same MMRM and ANCOVA models described above were used for ppFEV1 and LCI outcomes, respectively. Individual patient data were excluded based on the following criteria: AEs that could have affected lung function, low (<80%) treatment compliance and unacceptable pulmonary function test quality. These criteria, examined during a blinded medical review, were discussed and

identified in advance. The assumption was that the impact of these criteria on the overall changes in $ppFEV_1$ could be greater than the individual treatment effect size in the 4-week treatment duration (only Week 1 and Week 4 with lung function measurements). After data were reviewed by an Interim Analysis Assessment Committee at the interim futility analysis, a second analysis, a *post hoc* (after unblinding) quantile regression, was carried out to measure median change from baseline to Week 4 in $ppFEV_1$ and LCI in the BI 1265162 200 µg BID and placebo treatment groups. The third analysis was a combination of analyses 1 and 2, whereby a *post hoc* (after unblinding) quantile regression was carried out and patient data were excluded as described above.

Subgroup analysis

A model-based predefined subgroup analysis was performed to investigate any impact of patient characteristics, CFTR mutation status and concomitant CF therapy use on the change from baseline in trough $ppFEV_1$ after 4 weeks of treatment.

Ethics

The protocol was reviewed and approved by the respective Institutional Review Boards/Independent Ethics Committees of the participating centres. The study was carried out in accordance with the principles of the Declaration of Helsinki, in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH GCP), and in accordance with applicable regulatory requirements.

Prior to patient participation in the study, written informed consent was obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country.

Funding of study

The study was funded by Boehringer Ingelheim.

Results

Supplementary tables

Supplementary Table S1. Patients with visit data exclusions in the sensitivity analyses – TS

Treatment group	Patient	Reason	Visit	PT/comment
Placebo	1250008002	AE[1]	Week 1 Week 4	Bronchial congestion
	1250008003	AE[1]	Week 4	Bronchial infection
	1840004001	AE[1]	Week 4	Reactive airway disease exacerbation
	1840004002	AE[1]	Week 4	Cough increased and sputum increased
BI 200 µg	1250008001	AE[1]	Week 4	Spastic bronchial infection
	1276002003	AE[1]	Week 4	Lung infection with *Prevotella melaninogenica*
	1840008002	AE[1]	Baseline Week 1 Week 4	Lung congestion
	1250010002	Insufficient treatment compliance[2]	Week 4	Overall treatment compliance 70%
	1840006001	Unacceptable pulmonary test quality[3]	Baseline Week 1 Week 4	Pre-existing tracheomalacia

[1]Ongoing AE potentially affecting lung function.
[2]Insufficient treatment compliance was defined as compliance <80%.
[3]Unacceptable pulmonary function test quality at baseline and baseline condition considered as important protocol deviation.
AE: adverse event; BI: BI 1265162; PT; preferred term; TS: treated set.

Supplementary Table S2. Summary of baseline and changes from baseline after 4 weeks of treatment in CFQ-R total and Respiratory Domain scores (descriptive statistics) – TS

	CFQ-R total score							CFQ-R Respiratory Domain score						
	Baseline score				Change from baseline after 4 weeks			Baseline score				Change from baseline after 4 weeks		
	N	Mean	SD		N	Mean	SD	N	Mean	SD		N	Mean	SD
Placebo	18	886.296	163.999		18	5.941	79.669	18	69.444	21.495		18	–2.778	18.597
BI 20 µg	6	913.704	112.614		4	27.083	61.626	6	75.000	24.024		4	6.944	5.319
BI 50 µg	5	991.556	124.086		5	11.167	33.968	5	70.000	11.520		5	–2.222	10.092
BI 100 µg	5	878.333	298.360		5	–15.611	62.167	5	61.111	31.427		5	6.667	13.264
BI 200 µg	17	891.797	128.464		16	24.236	58.290	17	63.399	16.204		16	6.597	14.937

BI: BI 1265162; CFQ-R: Cystic Fibrosis Questionnaire – Revised; SD: standard deviation; TS: treated set.

Supplementary Table S3. Summary of baseline and changes from baseline after 4 weeks of treatment in the four separate subscores of the CASA-Q© (descriptive statistics) – TS

	N	Mean	(SD)	N	Mean	(SD)
Cough Symptom Domain Score						
Placebo	18	57.870	(22.592)	18	4.167	(18.798)
BI 20 µg	6	65.278	(24.954)	4	10.417	(17.180)
BI 50 µg	5	56.667	(19.896)	5	8.333	(8.333)
BI 100 µg	5	56.667	(31.402)	5	3.333	(24.008)
BI 200 µg	18	54.167	(22.002)	17	5.392	(15.574)
Cough Impact Domain Score						
Placebo	18	83.681	(15.104)	18	–0.521	(16.648)
BI 20 µg	6	90.625	(6.555)	4	–6.250	(12.758)
BI 50 µg	5	85.000	(16.741)	5	–0.625	(12.771)
BI 100 µg	5	76.875	(32.067)	5	1.250	(14.757)
BI 200 µg	18	84.722	(12.768)	17	0.735	(11.187)
Sputum Symptom Domain Score						
Placebo	18	55.556	(17.620)	18	5.093	(15.950)
BI 20 µg	6	65.278	(25.504)	4	4.167	(8.333)
BI 50 µg	5	60.000	(27.259)	5	10.000	(14.907)
BI 100 µg	5	63.333	(13.944)	5	3.333	(16.245)
BI 200 µg	18	61.574	(17.419)	17	5.392	(19.530)
Sputum Impact Domain Score						
Placebo	18	83.102	(12.250)	18	–0.694	(16.497)
BI 20 µg	6	90.278	(10.092)	4	–4.167	(3.402)
BI 50 µg	5	82.500	(23.459)	5	5.000	(11.562)
BI 100 µg	5	81.667	(36.515)	5	–0.833	(13.944)
BI 200 µg	18	86.343	(11.236)	17	0.490	(11.110)

BI, BI 1265162; CASA-Q©: Cough and Sputum Assessment Questionnaire; SD: standard deviation; TS: treated set.

Supplementary Table S4. Pharmacokinetic parameters (N, gMean, gCV) of twice-daily BI 1265162 by treatment group – PKS

	BI 20 µg				BI 50 µg				BI 100 µg				BI 200 µg		
	N	gMean[1]	gCV[2]		N	gMean[1]	gCV[2]		N	gMean[1]	gCV[2]		N	gMean[1]	gCV[2]
$C_{0.083}$	4	131	106		2	-	-		4	732	12.0		16	1000	106
$C_{0.083,ss,15}$	3	207	59.9		4	471	30.0		4	1010	20.1		16	1110	84.8
$C_{0.083,ss,57}$	3	162	76.3		3	463	15.4		5	573	94.0		14	1080	165
$C_{pre,ss,15}$	3	7.82	28.0		4	24.3	31.8		5	38.4	292		14	43.8	95.6
$C_{pre,ss,57}$	1	-	-		3	13.0	80.8		3	22.3	48.3		12	37.2	56.9
$C_{max,ss,15}$	5	163	57.0		4	471	30.0		4	1010	20.1		17	1120	81.5
$AUC_{0-4,ss,15}$	5	192	45.3		4	541	19.1		4	1020	8.93		17	1380	71.0

[1]Units were pmol/L for $C_{0.083}$, $C_{0.083,ss,15}$, $C_{0.083,ss,57}$, $C_{pre,ss,15}$, $C_{pre,ss,57}$, $C_{max,ss,15}$ and h×pmol/L for $AUC_{0-4,ss,15}$.

[2]Units were % for gCV.

$AUC_{0-4,ss,15}$: area under the curve from 0 to 4 h at steady state after dose 15; BI: BI 1265162; $C_{0.083}$:concentration at time 0.083 h; $C_{0.083,ss,15}$: concentration at time 0.083 h at steady state after dose 15; $C_{0.083,ss,57}$: concentration at time 0.083 h at steady state after dose 57; $C_{pre,ss,15}$: pre-dose concentration at steady state for dose 15; $C_{pre,ss,57}$: pre-dose concentration at steady state for dose 57; $C_{max,ss,15}$: maximum measured concentration at steady state following dose 15; gCV: geometric coefficient of variation; gMean: geometric mean; PKS: pharmacokinetics set.

.

References

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