Clinical trial results:
A multicentre, randomised, double-blind, active-controlled, 3-way cross-over study to evaluate the efficacy and safety of a free combination of 3 doses of CHF 5259 (glycopyrrolate) plus Foster® 100/6µg (fixed combination of beclomethasone dipropionate plus formoterol) in a metered dose inhaler for the treatment of patients with uncontrolled asthma under medium doses of inhaled corticosteroids plus long-acting 2-agonists

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2013-003043-36
Trial protocol	DE GB HU IT PL BG
Global end of trial date	08 March 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	CCD-1206-PR-0088

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02127866
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, CHIESI FARMACEUTICI S.p.A, clinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, CHIESI FARMACEUTICI S.p.A, ClinicalTrial_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 March 2015
Global end of trial reached?	Yes
Global end of trial date	08 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a free combination of CHF 5259 (glycopyrrolate bromide [GB]) at 3 dose levels plus Foster 100/6 µg (fixed combination of beclomethasone dipropionate [BDP] plus formoterol [FF]) in a pressurised metered dose inhaler by comparison with Foster 100/6 µg in terms of FEV1 AUC0-12h normalised by time on Day 42.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator:

Foster® 100/6µg (fixed combination of beclometasone dipropionate plus formoterol) administered via pMDI.

Actual start date of recruitment	11 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 62
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 48
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Hungary: 59
Country: Number of subjects enrolled	Italy: 5
Worldwide total number of subjects	211
EEA total number of subjects	211

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	186
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multinational study was conducted at 44 clinical sites (43 active) in 6 countries. The recruitment took place in:
Bulgaria (10 sites)
Germany (8 sites)
Hungary (7 sites)
Italy (5 sites: 4 active and 1 non-active)
Poland (12 sites)
UK (2 sites)

Pre-assignment

Screening details:

A total of 322 patients were screened, of whom 211 were randomised to one of the following treatment sequence groups:
•Sequence A-C-B: n = 53;
•Sequence B-D-C: n = 53;
•Sequence C-A-D: n = 53;
•Sequence D-B-A: n = 52.
201 (95.3%) patients completed the study.

Period 1

Period 1 title	Overall trial by sequence (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

To maintain the blind during the treatment period, patients inhaled study medication from four identical white canisters daily, regardless of treatment regimen. The randomisation list was provided to the labelling facility but was not available to patients, investigators, monitors or employees of CROMSOURCE involved in the management of the trial before unblinding of the data, unless in case of emergency. The Sponsor's clinical team was also blinded during the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A-C-B

Arm description:

Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.
Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg.

Arm type	Experimental
Investigational medicinal product name	CHF 5259 pMDI
Investigational medicinal product code	
Other name	glycopyrronium bromide [GB]
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

• Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
• Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
• Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.

Investigational medicinal product name	Foster® 100/6 µg pMDI
Investigational medicinal product code	
Other name	fixed dose combination [FDC] of beclometasone dipropionate [BDP] plus formoterol [FF]
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

• Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
• Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
• Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.

Arm title	Sequence B-D-C

Arm description:

Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg.
Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.

Arm type	Experimental
Investigational medicinal product name	CHF 5259 pMDI
Investigational medicinal product code	
Other name	glycopyrronium bromide [GB]
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

• Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
• Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg; or
• Treatment D: two puffs of CHF 5259 placebo BID (plus Foster alone).

Investigational medicinal product name	Foster® 100/6 µg pMDI
Investigational medicinal product code	
Other name	fixed dose combination [FDC] of beclometasone dipropionate [BDP] plus formoterol [FF]
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

• Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
• Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.
• Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg.

Arm title	Sequence C-A-D

Arm description:

Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.
Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg.

Arm type	Experimental

Investigational medicinal product name	CHF 5259 pMDI
Investigational medicinal product code	
Other name	glycopyrronium bromide [GB]
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

• Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
• Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg; or
• Treatment D: two puffs of CHF 5259 placebo BID (plus Foster alone).

Investigational medicinal product name	Foster® 100/6 µg pMDI
Investigational medicinal product code	
Other name	fixed dose combination [FDC] of beclometasone dipropionate [BDP] plus formoterol [FF]
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

• Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
• Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.
• Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg.

Arm title	Sequence D-B-A

Arm description:

Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg;
Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg.

Arm type	Experimental
Investigational medicinal product name	CHF 5259 pMDI
Investigational medicinal product code	
Other name	glycopyrronium bromide [GB]
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

• Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
• Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
• Treatment D: two puffs of CHF 5259 placebo BID (plus Foster alone).

Investigational medicinal product name	Foster® 100/6 µg pMDI
Investigational medicinal product code	
Other name	fixed dose combination [FDC] of beclometasone dipropionate [BDP] plus formoterol [FF]
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

• Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
• Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
• Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg.

Number of subjects in period 1	Sequence A-C-B	Sequence B-D-C	Sequence C-A-D
Started	53	53	53
Completed	51	52	49
Not completed	2	1	4
Consent withdrawn by subject	-	-	2
Other	1	-	1
Protocol deviation	1	1	1

Number of subjects in period 1	Sequence D-B-A
Started	52
Completed	49
Not completed	3
Consent withdrawn by subject	3
Other	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Sequence A-C-B
Reporting group description:	
Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg; Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg. Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg.	
Reporting group title	Sequence B-D-C
Reporting group description:	
Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg; Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg. Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.	
Reporting group title	Sequence C-A-D
Reporting group description:	
Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg. Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg; Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg.	
Reporting group title	Sequence D-B-A
Reporting group description:	
Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg; Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg; Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg.	

Reporting group values	Sequence A-C-B	Sequence B-D-C	Sequence C-A-D
Number of subjects	53	53	53
Age categorical Units: Subjects			
Adults (18-64 years)	47	49	46
From 65-84 years	6	4	7
Age continuous Units: years			
arithmetic mean	51.3	51.2	51.5
standard deviation	± 12.3	± 11.1	± 13.8
Gender categorical Units: Subjects			
Female	38	40	30
Male	15	13	23

Reporting group values	Sequence D-B-A	Total	
Number of subjects	52	211	

Age categorical Units: Subjects			
Adults (18-64 years)	44	186	
From 65-84 years	8	25	
Age continuous Units: years			
arithmetic mean	49.3		
standard deviation	± 13.9	-	
Gender categorical Units: Subjects			
Female	27	135	
Male	25	76	

End points reporting groups

Reporting group title	Sequence A-C-B

Reporting group description:

Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.
Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg.

Reporting group title	Sequence B-D-C

Reporting group description:

Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg.
Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.

Reporting group title	Sequence C-A-D

Reporting group description:

Treatment C: two puffs of CHF 5259 25 µg BID + two puffs of Foster® 100 /6 µg BID – total daily dose of CHF 5259 100 µg + Foster® 400 µg/24 µg.
Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg;
Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg.

Reporting group title	Sequence D-B-A

Reporting group description:

Treatment D: two puffs of CHF 5259 placebo BID and two puffs of Foster® 100 µg/6 µg BID – total daily dose of Foster® 400 µg/24 µg;
Treatment B: one puff of CHF 5259 25 µg BID + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 50 µg + Foster® 400 µg/24 µg;
Treatment A: one puff of CHF 5259 12.5 µg twice a day (BID) + one puff of CHF 5259 placebo BID + two puffs of Foster® 100 µg/6 µg BID – total daily dose of CHF 5259 25 µg + Foster® 400 µg/24 µg.

Subject analysis set title	Treatment A - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention-to-Treat (ITT) population: all randomised patients who received at least one dose of the study treatment and with at least one available evaluation of efficacy after the Baseline were included in the ITT population.

Subject analysis set title	Treatment A - safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population: all randomised patients who received at least one dose of study treatment were included in the safety population.

Subject analysis set title	Treatment B - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention-to-Treat (ITT) population: all randomised patients who received at least one dose of the study treatment and with at least one available evaluation of efficacy after the Baseline were included in the ITT population.

Subject analysis set title	Treatment B - safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population: all randomised patients who received at least one dose of study treatment were included in the safety population.

Subject analysis set title	Treatment C - ITT population

Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention-to-Treat (ITT) population: all randomised patients who received at least one dose of the study treatment and with at least one available evaluation of efficacy after the Baseline were included in the ITT population.

Subject analysis set title	Treatment C - safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population: all randomised patients who received at least one dose of study treatment were included in the safety population.

Subject analysis set title	Treatment D - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention-to-Treat (ITT) population: all randomised patients who received at least one dose of the study treatment and with at least one available evaluation of efficacy after the Baseline were included in the ITT population.

Subject analysis set title	Treatment D - safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population: all randomised patients who received at least one dose of study treatment were included in the safety population.

Primary: FEV1 AUC0-12h normalised by time on Day 42

End point title	FEV1 AUC0-12h normalised by time on Day 42

End point description:

AUC0-12= area under the curve between the time 0 and 12 hours.
Post-dose FEV1 on Day 42 of each treatment period was recorded at 15'; 30'; 45'; 1h; 2h; 3h, 4h,6h, 8h, 11h30 and 12h post-study drug intake. The baseline FEV1 was the average FEV1 recorded on Day 1 at 45 and 10 minutes prior to study intake.

End point type	Primary

End point timeframe:

On Day 42

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[1]	150[2]	152[3]	152[4]
Units: liters				
arithmetic mean (standard deviation)	2.327 (± 0.751)	2.332 (± 0.752)	2.272 (± 0.717)	2.296 (± 0.692)

Notes:

[1] - This is the actual number of patients on which the analysis was performed.

[2] - This is the actual number of patients on which the analysis was performed.

[3] - This is the actual number of patients on which the analysis was performed.

[4] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.096

Notes:

[5] - FEV1 AUC0-12h normalized by time at Day 42 will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average of the FEV1 pre-dose measurements on Day 1 of each treatment period) as a covariate. The adjusted mean differences between each dose level of the free combination and Foster alone will be calculated with their simultaneous 95% confidence intervals (CIs) and p-values.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.047
upper limit	0.121

Notes:

[6] - FEV1 AUC0-12h normalized by time at Day 42 will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average of the FEV1 pre-dose measurements on Day 1 of each treatment period) as a covariate. The adjusted mean differences between each dose level of the free combination and Foster alone will be calculated with their simultaneous 95% confidence intervals (CIs) and p-values.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population

Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.047
upper limit	0.121

Notes:

[7] - FEV1 AUC0-12h normalized by time at Day 42 will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average of the FEV1 pre-dose measurements on Day 1 of each treatment period) as a covariate. The adjusted mean differences between each dose level of the free combination and Foster alone will be calculated with their simultaneous 95% confidence intervals (CIs) and p-values.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=299 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.113
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.057

Notes:

[8] - FEV1 AUC0-12h normalized by time at Day 42 will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average of the FEV1 pre-dose measurements on Day 1 of each treatment period) as a covariate. The adjusted mean differences between each higher dose of the free combination (Treatment B and Treatment C) and the lowest dose of the free combination (Treatment A) will be calculated with their simultaneous 95% CIs and p-values.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.106
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.026

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.057

Notes:

[9] - FEV1 AUC0-12h normalized by time at Day 42 will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average of the FEV1 pre-dose measurements on Day 1 of each treatment period) as a covariate. The adjusted mean differences between each higher dose of the free combination (Treatment B and Treatment C) and the lowest dose of the free combination (Treatment A) will be calculated with their simultaneous 95% CIs and p-values.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.983
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.031

Notes:

[10] - FEV1 AUC0-12h normalized by time at Day 42 will be analysed using an ANCOVA model including treatment, period and patient as fixed effects and baseline (average of the FEV1 pre-dose measurements on Day 1 of each treatment period) as a covariate. The adjusted mean differences between each higher dose of the free combination (Treatment B and Treatment C) and the lowest dose of the free combination (Treatment A) will be calculated with their simultaneous 95% CIs and p-values.

Secondary: Change from baseline in peak FEV1 on Day 42

End point title	Change from baseline in peak FEV1 on Day 42

End point description:

The maximum FEV1 value obtained between 15 minutes and 12 hours post-dose is the peak FEV1.
Post-dose FEV1 on Day 42 of each treatment period was recorded at 15’; 30’; 45’; 1h; 2h; 3h, 4h,6h, 8h, 11h30 and 12h post-study drug intake.
Baseline is the average of the FEV1 pre-dose measurements on Day 1 of each period (recorded at 45 and 10 minuted prior to study drug intake).

End point type	Secondary

End point timeframe:

On Day 42.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[11]	152[12]	153[13]	152[14]
Units: liters				
arithmetic mean (standard deviation)	0.438 (± 0.34)	0.463 (± 0.327)	0.418 (± 0.327)	0.396 (± 0.3)

Notes:

[11] - This is the actual number of patients on which the analysis was performed.

[12] - This is the actual number of patients on which the analysis was performed.

[13] - This is the actual number of patients on which the analysis was performed.

[14] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	least square mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.098

Notes:

[15] - The key secondary efficacy variable (i.e. change from Baseline in peak FEV1 on Day 42) was analysed on both the ITT and the PP populations using the ANCOVA model described for the primary efficacy variable.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.091

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.054
upper limit	0.128

Notes:

[16] - The key secondary efficacy variable (i.e. change from Baseline in peak FEV1 on Day 42) was analysed on both the ITT and the PP populations using the ANCOVA model described for the primary efficacy variable

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.113

Notes:

[17] - The key secondary efficacy variable (i.e. change from Baseline in peak FEV1 on Day 42) was analysed on both the ITT and the PP populations using the ANCOVA model described for the primary efficacy variable.

Statistical analysis title	treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.051
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.062

Notes:

[18] - The key secondary efficacy variable (i.e. change from Baseline in peak FEV1 on Day 42) was analysed on both the ITT and the PP populations using the ANCOVA model described for the primary efficacy variable.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment C - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.32
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.047

Notes:

[19] - The key secondary efficacy variable (i.e. change from Baseline in peak FEV1 on Day 42) was analysed on both the ITT and the PP populations using the ANCOVA model described for the primary efficacy variable.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.332
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.016

Notes:

[20] - The key secondary efficacy variable (i.e. change from Baseline in peak FEV1 on Day 42) was analysed on both the ITT and the PP populations using the ANCOVA model described for the primary efficacy variable

Secondary: FEV1 AUC0-3h normalised by time on Day 1

End point title	FEV1 AUC0-3h normalised by time on Day 1

End point description:

AUC0-3h = area under the curve between time 0 and 3 hours.
The pre-dose and post-dose lung function assessments were recorded under supervision at the following

timings:
•Pre-dose FEV1 on Day 1 at 45 and 10 minutes prior to study drug intake (baseline FEV1);
•Post-dose FEV1 on Day 1 of each treatment period: at 15’; 30’; 45’; 1h; 2h; 3h post-study drug intake.

End point type	Secondary
End point timeframe:	
On Day 1	

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[21]	153[22]	155[23]	152[24]
Units: liters				
arithmetic mean (standard deviation)	2.379 (± 0.741)	2.366 (± 0.758)	2.311 (± 0.7)	2.364 (± 0.717)

Notes:

[21] - This is the actual number of patients on which the analysis was performed.

[22] - This is the actual number of patients on which the analysis was performed.

[23] - This is the actual number of patients on which the analysis was performed.

[24] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.079

Notes:

[25] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment D - ITT population v Treatment B - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.079

Notes:

[26] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.083

Notes:

[27] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.995
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.03

Notes:

[28] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.778
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.034

Notes:

[29] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=308 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.771
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.034

Notes:

[30] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates

Secondary: FEV1 AUC0-3h normalised by time on Day 42

End point title	FEV1 AUC0-3h normalised by time on Day 42

End point description:

AUC0-3h = area under the curve between time 0 and 3 hours.
The pre-dose and post-dose lung function assessments were recorded under supervision at the following timings:
•Pre-dose FEV1 on Day 1 at 45 and 10 minutes prior to study drug intake (baseline FEV1);
•Post-dose FEV1 on Day 42 of each treatment period: at 15'; 30'; 45'; 1h; 2h; 3h post-study drug intake.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[31]	152[32]	152[33]	152[34]
Units: liters				
arithmetic mean (standard deviation)	2.389 (± 0.763)	2.415 (± 0.764)	2.342 (± 0.727)	2.367 (± 0.703)

Notes:

[31] - This is the actual number of patients on which the analysis was performed.

[32] - This is the actual number of patients on which the analysis was performed.

[33] - This is the actual number of patients on which the analysis was performed.

[34] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.089

Notes:

[35] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set)

is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.124

Notes:

[36] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	0.122

Notes:

[37] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.029
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.036

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.069

Notes:

[38] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.044
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.066

Notes:

[39] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment B - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.859
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	0.029

Notes:

[40] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: Change from baseline in FEV1 pre-dose on Day 14

End point title	Change from baseline in FEV1 pre-dose on Day 14

End point description:

The pre-dose morning FEV1 is defined as the mean of the two measurements at 45 and 10 minutes pre-dose.

End point type	Secondary

End point timeframe:

On Day 14

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152[41]	155[42]	155[43]	152[44]
Units: liters				
arithmetic mean (standard deviation)	0.082 (± 0.279)	0.103 (± 0.281)	0.085 (± 0.267)	0.08 (± 0.25)

Notes:

[41] - This is the actual number of patients on which the analysis was performed.

[42] - This is the actual number of patients on which the analysis was performed.

[43] - This is the actual number of patients on which the analysis was performed.

[44] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.168
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.075

Notes:

[45] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.016
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.096

Notes:

[46] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.058
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.086

Notes:

[47] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.315
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.022

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.066

Notes:

[48] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.607
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.055

Notes:

[49] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=310 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.621
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.054
upper limit	0.032

Notes:

[50] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: Change from baseline in FEV1 pre-dose on Day 42

End point title	Change from baseline in FEV1 pre-dose on Day 42

End point description:

The pre-dose morning FEV1 is defined as the mean of the two measurements at 45 and 10 minutes pre-dose.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[51]	153[52]	155[53]	152[54]
Units: liters				
arithmetic mean (standard deviation)	0.048 (± 0.298)	0.087 (± 0.299)	0.072 (± 0.295)	0.067 (± 0.273)

Notes:

[51] - This is the actual number of patients on which the analysis was performed.

[52] - This is the actual number of patients on which the analysis was performed.

[53] - This is the actual number of patients on which the analysis was performed.

[54] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.484
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.058

Notes:

[55] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.005
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.102

Notes:

[56] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.016
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.094

Notes:

[57] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.038
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.045

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.087

Notes:

[58] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.087
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.079

Notes:

[59] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=308 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.709
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.034

Notes:

[60] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: Change from baseline in through FEV1 at 12 h post-dose on Day 1

End point title	Change from baseline in through FEV1 at 12 h post-dose on Day 1

End point description:

Trough FEV1 at 12 hours is determined as the average of the 11.5 and 12 hours post-dose FEV1 assessments. Baseline value is the mean of the pre-dose measurement of FEV1 at Day 1 of each treatment period recorded at 45 and 10 minutes prior to study drug intake.

End point type	Secondary

End point timeframe:

On Day 1

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[61]	153[62]	156[63]	149[64]
Units: liters				
arithmetic mean (standard deviation)	0.146 (± 0.294)	0.137 (± 0.262)	0.138 (± 0.266)	0.127 (± 0.273)

Notes:

[61] - This is the actual number of patients on which the analysis was performed.

[62] - This is the actual number of patients on which the analysis was performed.

[63] - This is the actual number of patients on which the analysis was performed.

[64] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=299 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority[65]
P-value	= 0.159
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.011
upper limit	0.067

Notes:

[65] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.089
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.072

Notes:

[66] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	= 0.008
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.091

Notes:

[67] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 0.781
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.005

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.044

Notes:

[68] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.205
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.063

Notes:

[69] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	= 0.32
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.019
upper limit	0.057

Notes:

[70] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: Change from baseline in through FEV1 at 12 h post-dose on Day 42

End point title	Change from baseline in through FEV1 at 12 h post-dose on Day 42

End point description:

Trough FEV1 at 12 hours is determined as the average of the 11.5 and 12 hours post-dose FEV1 assessments. Baseline value is the mean of the pre-dose measurement of FEV1 at Day 1 of each treatment period recorded at 45 and 10 minutes prior to study drug intake.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[71]	150[72]	154[73]	152[74]
Units: liters				
arithmetic mean (standard deviation)	0.143 (± 0.345)	0.143 (± 0.297)	0.135 (± 0.308)	0.109 (± 0.28)

Notes:

[71] - This is the actual number of patients on which the analysis was performed.

[72] - This is the actual number of patients on which the analysis was performed.

[73] - This is the actual number of patients on which the analysis was performed.

[74] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment D - ITT population v Treatment A - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[75]
P-value	= 0.015
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.083

Notes:

[75] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	= 0.008
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.087

Notes:

[76] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[77]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.105

Notes:

[77] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=299 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	= 0.832
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.004

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.041

Notes:

[78] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[79]
P-value	= 0.234
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.059

Notes:

[79] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment B - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	= 0.328
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.055

Notes:

[80] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: Change from baseline in peak FEV1 on Day 1

End point title	Change from baseline in peak FEV1 on Day 1

End point description:

The peak FEV1 is the maximum FEV1 value obtained between 15 minutes and 12 hours post-dose. Post-dose FEV1 on Day 1 of each treatment period was recorded at 15'; 30'; 45'; 1h; 2h; 3h, 4h,6h, 8h, 11h30 and 12h post-study drug intake.
Baseline is the average of the FEV1 pre-dose measurements on Day 1 of each period (recorded at 45 and 10 minuted prior to study drug intake).

End point type	Secondary

End point timeframe:

On Day 1

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[81]	153[82]	156[83]	153[84]
Units: liters				
arithmetic mean (standard deviation)	0.455 (± 0.308)	0.441 (± 0.278)	0.424 (± 0.26)	0.408 (± 0.252)

Notes:

[81] - This is the actual number of patients on which the analysis was performed.

[82] - This is the actual number of patients on which the analysis was performed.

[83] - This is the actual number of patients on which the analysis was performed.

[84] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[85]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.094

Notes:

[85] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[86]
P-value	= 0.012
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.081

Notes:

[86] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[87]
P-value	= 0.004
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.088

Notes:

[87] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[88]
P-value	= 0.492
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.012

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.023

Notes:

[88] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a Cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[89]
P-value	= 0.772
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.03

Notes:

[89] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and Baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[90]
P-value	= 0.689
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.042

Notes:

[90] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: FEV1 AUC0-12h normalised by time on Day 1

End point title	FEV1 AUC0-12h normalised by time on Day 1

End point description:

AUC0-12h = area under the curve between time 0 and 12 hours.
Post-dose FEV1 on Day 1 of each treatment period was recorded at 15'; 30'; 45'; 1h; 2h; 3h, 4h,6h, 8h, 11h30 and 12h post-study drug intake. The baseline FEV1 was the average FEV1 recorded on Day 1 at 45 and 10 minutes prior to study intake.

End point type	Secondary

End point timeframe:

On Day 1

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[91]	152[92]	154[93]	148[94]
Units: liters				
arithmetic mean (standard deviation)	2.33 (± 0.742)	2.313 (± 0.754)	2.26 (± 0.693)	2.329 (± 0.708)

Notes:

[91] - This is the actual number of patients on which the analysis was performed.

[92] - This is the actual number of patients on which the analysis was performed.

[93] - This is the actual number of patients on which the analysis was performed.

[94] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=297 (subject analysis set) is an innate error of the EudraCT database system

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority[95]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.082

Notes:

[95] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=300 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	superiority[96]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.083

Notes:

[96] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[97]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.096

Notes:

[97] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[98]
P-value	= 0.972
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.001

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.031

Notes:

[98] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[99]
P-value	= 0.375
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.045

Notes:

[99] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment B - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[100]
P-value	= 0.389
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.044

Notes:

[100] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: FEV1 percentage of predicted normal value at each time point post-dose

on Day 1 and mean changes from Baseline

End point title	FEV1 percentage of predicted normal value at each time point post-dose on Day 1 and mean changes from Baseline

End point description:

Baseline is the average of the pre-dose measurements of FEV1 Percentage of Predicted Normal Value.
Measurements were done: 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 11h and 30 min, 12h post-dose on Day 1.
Only data about the change from baseline at the last timepoint (12h post-dose) of the Day 1 are reported in the database.
For the data about the other timepoints on Day 1 see pdf attached.

End point type	Secondary

End point timeframe:

On Day 1

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[101]	153[102]	156[103]	149[104]
Units: percentage				
arithmetic mean (standard deviation)	4.6 (± 8.5)	4.3 (± 8.7)	4.4 (± 8.6)	3.6 (± 8.3)

Notes:

[101] - This is the actual number of patients on which the analysis was performed.

[102] - This is the actual number of patients on which the analysis was performed.

[103] - This is the actual number of patients on which the analysis was performed.

[104] - This is the actual number of patients on which the analysis was performed.

Attachments (see zip file)	FEV1 Change D1.pdf FEV1 Value D1.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 percentage of predicted normal value at 2h post-dose on Day 14 and mean changes from Baseline

End point title	FEV1 percentage of predicted normal value at 2h post-dose on Day 14 and mean changes from Baseline

End point description:

Baseline is the average of the pre-dose measurements of FEV1 Percentage of Predicted Normal Value.
Measurements were done 2h post-dose on Day 14.
Only the change from baseline (not the actual value) is reported in the database. For the actual values on the same endpoint , please see the pdf attached.

End point type	Secondary

End point timeframe:

On Day 14

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152[105]	155[106]	155[107]	152[108]
Units: percentage				
arithmetic mean (standard deviation)	11.5 (± 9.5)	11.7 (± 9.9)	10.8 (± 9.1)	9.2 (± 9.5)

Notes:

[105] - This is the actual number of patients on which the analysis was performed.

[106] - This is the actual number of patients on which the analysis was performed.

[107] - This is the actual number of patients on which the analysis was performed.

[108] - This is the actual number of patients on which the analysis was performed.

Attachments (see zip file)	FEV1 Value D14.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 percentage of predicted normal value at each time point post-dose on Day 42 and mean changes from Baseline

End point title	FEV1 percentage of predicted normal value at each time point post-dose on Day 42 and mean changes from Baseline

End point description:

Baseline is the average of the pre-dose measurements of FEV1 Percentage of Predicted Normal Value.
Measurements were done: 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 11h and 30 min, 12h post-dose on Day 42.
Only data about the change from baseline at the last timepoint (12h post-dose) of the Day 42 are reported in the database.
For the data about the other timepoints on Day 42, please see the pdf attached.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[109]	150[110]	154[111]	152[112]
Units: percentage				
arithmetic mean (standard deviation)	4.5 (± 10.2)	4.5 (± 9.5)	4.3 (± 10.1)	3.4 (± 8.7)

Notes:

[109] - This is the actual number of patients on which the analysis was performed.

[110] - This is the actual number of patients on which the analysis was performed.

[111] - This is the actual number of patients on which the analysis was performed.

[112] - This is the actual number of patients on which the analysis was performed.

Attachments (see zip file)	FEV1 changes D42.pdf FEV1 Value D42.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 at 2 hours post-dose on Day 14

End point title	FEV1 at 2 hours post-dose on Day 14

End point description:

Post dose FEV1 on Day 14 of each treatment period was recorded at 2h post-study drug intake.

End point type	Secondary

End point timeframe:

On Day 14

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	155[113]	155[114]	152[115]
Units: liters				
arithmetic mean (standard deviation)	2.429 (± 0.744)	2.426 (± 0.782)	2.365 (± 0.739)	2.388 (± 0.704)

Notes:

[113] - This is the actual number of patients on which the analysis was performed.

[114] - This is the actual number of patients on which the analysis was performed.

[115] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FEV1 2 Hours Post-Dose on Day 14

End point title	Change from baseline in FEV1 2 Hours Post-Dose on Day 14

End point description:

Baseline is the average of the pre-dose measurements FEV1 measurements that were recorded at 45 and 10 minutes prior to study intake.
Post dose FEV1 on Day 14 of each treatment period was recorded at 2h post-study drug intake.

End point type	Secondary

End point timeframe:

On Day 14

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	155[116]	155[117]	152[118]
Units: liters				
arithmetic mean (standard deviation)	0.362 (± 0.324)	0.364 (± 0.329)	0.335 (± 0.291)	0.298 (± 0.312)

Notes:

[116] - This is the actual number of patients on which the analysis was performed.

[117] - This is the actual number of patients on which the analysis was performed.

[118] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Average daily morning PEF

End point title	Average daily morning PEF

End point description:

E-peakflow meter/e-diary was completed at home on a daily basis morning and evening (daily download of the e-peakflow meter/e-diary). During the two wash-out periods, only the compliance to the wash-out medication was collected.
During the run-in period and the three treatment periods, PEF (L/min) was monitored twice daily before the intake of the run-in medication or study medication. Morning measurements were done approximately between 7:00 am and 9:00 am and evening measurements approximately between 7:00 pm and 9:00 pm. An alarm reminded the patients to perform measurements. During each measurement session, the patient performed three blows and data were recorded in the device.

End point type	Secondary

End point timeframe:

Daily during run-in and treatment periods.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	153[119]	155[120]	151[121]
Units: L/min				
arithmetic mean (standard deviation)	342.16 (± 115)	339.41 (± 111.42)	337.26 (± 112.33)	339.89 (± 108.66)

Notes:

[119] - This is the actual number of patients on which the analysis was performed.

[120] - This is the actual number of patients on which the analysis was performed.

[121] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[122]
P-value	< 0.001
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	10.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.52
upper limit	14.63

Notes:

[122] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[123]
P-value	< 0.001
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	11.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.6
upper limit	15.64

Notes:

[123] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[124]
P-value	< 0.001
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	9.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.98
upper limit	14

Notes:

[124] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[125]
P-value	= 0.649
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.47
upper limit	5.57

Notes:

[125] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system

Comparison groups	Treatment A - ITT population v Treatment C - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[126]
P-value	= 0.798
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.09
upper limit	3.92

Notes:

[126] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=308 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority[127]
P-value	= 0.474
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-1.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.12
upper limit	2.85

Notes:

[127] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Secondary: Average daily evening PEF

End point title	Average daily evening PEF

End point description:

E-peakflow meter/e-diary was completed at home on a daily basis morning and evening (daily download of the e-peakflow meter/e-diary). During the two wash-out periods, only the compliance to the wash-out medication was collected.
During the run-in period and the three treatment periods, PEF (L/min) was monitored twice daily before the intake of the run-in medication or study medication. Morning measurements were done approximately between 7:00 am and 9:00 am and evening measurements approximately between 7:00 pm and 9:00 pm. An alarm reminded the patients to perform measurements. During each measurement session, the patient performed three blows and data were recorded in the device.

End point type	Secondary

End point timeframe:

Daily during run-in and treatment periods.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	153[128]	155[129]	152[130]
Units: L/min				
arithmetic mean (standard deviation)	353.45 (± 113.91)	351.65 (± 111.36)	348.04 (± 112.66)	348.02 (± 105.52)

Notes:

[128] - This is the actual number of patients on which the analysis was performed.

[129] - This is the actual number of patients on which the analysis was performed.

[130] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[131]
P-value	< 0.001
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	11.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	7.41
upper limit	16.47

Notes:

[131] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[132]
P-value	< 0.001
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	14.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.72
upper limit	18.72

Notes:

[132] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[133]
P-value	< 0.001
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	11.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.44
upper limit	16.44

Notes:

[133] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[134]
P-value	= 0.32
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	6.8

Notes:

[134] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment C - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[135]
P-value	= 0.999
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	4.5

Notes:

[135] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=308 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population

Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority[136]
P-value	= 0.317
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.76
upper limit	2.2

Notes:

[136] - This secondary efficacy variable was analysed on the ITT population using an ANOVA (analysis of variance) model including treatment, period and patient as fixed effects.

Secondary: Change from baseline in pre-dose FVC on Day 14

End point title	Change from baseline in pre-dose FVC on Day 14

End point description:

Pre-dose FVC was recorded on Day 14 at 45 minutes and 10 minutes prior to study drug intake.

End point type	Secondary

End point timeframe:

On Day 14

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	155[137]	155[138]	152[139]
Units: liters				
arithmetic mean (standard deviation)	0.07 (± 0.337)	0.149 (± 0.372)	0.087 (± 0.318)	0.081 (± 0.282)

Notes:

[137] - This is the actual number of patients on which the analysis was performed.

[138] - This is the actual number of patients on which the analysis was performed.

[139] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[140]
P-value	= 0.645
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.014

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.044
upper limit	0.072

Notes:

[140] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[141]
P-value	= 0.01
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.133

Notes:

[141] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[142]
P-value	= 0.508
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.077

Notes:

[142] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[143]
P-value	= 0.035
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.12

Notes:

[143] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment C - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[144]
P-value	= 0.842
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.052
upper limit	0.063

Notes:

[144] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=310 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority[145]
P-value	= 0.054
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.113
upper limit	0.001

Notes:

[145] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: Change from baseline in pre-dose FVC on Day 42

End point title	Change from baseline in pre-dose FVC on Day 42

End point description:

Pre-dose FVC was recorded on Day 42 at 45 minutes and 10 minutes prior to study drug intake.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[146]	153[147]	155[148]	152[149]
Units: liters				
arithmetic mean (standard deviation)	0.05 (± 0.367)	0.109 (± 0.378)	0.083 (± 0.308)	0.051 (± 0.327)

Notes:

[146] - This is the actual number of patients on which the analysis was performed.

[147] - This is the actual number of patients on which the analysis was performed.

[148] - This is the actual number of patients on which the analysis was performed.

[149] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	TReatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[150]
P-value	= 0.503
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.068

Notes:

[150] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and Baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[151]
P-value	= 0.046
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.102

Notes:

[151] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[152]
P-value	= 0.118
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.091

Notes:

[152] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[153]
P-value	= 0.188
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.085

Notes:

[153] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305(subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment C - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[154]
P-value	= 0.374
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.074

Notes:

[154] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=308 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority[155]
P-value	= 0.663
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.062
upper limit	0.039

Notes:

[155] - This secondary efficacy variable was analysed on the ITT population using ANCOVA model including treatment, period and patient as fixed effects and baseline values as covariates.

Secondary: Change from baseline in peak FVC on Day 1

End point title	Change from baseline in peak FVC on Day 1

End point description:

The peak FVC is the maximum FVC value obtained between 15 minutes and 12 hours post-dose.
Post-dose FVC on Day 1 of each treatment period was recorded at 15'; 30'; 45'; 1h; 2h; 3h, 4h,6h, 8h, 11h30 and 12h post-study drug intake.
Baseline is the average of the FVC pre-dose measurements on Day 1 of each period (recorded at 45 and 10 minuted prior to study drug intake).

End point type	Secondary

End point timeframe:

On Day 1.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[156]	153[157]	156[158]	153
Units: liters				
arithmetic mean (standard deviation)	0.435 (± 0.363)	0.433 (± 0.334)	0.421 (± 0.311)	0.388 (± 0.258)

Notes:

[156] - This is the actual number of patients on which the analysis was performed.

[157] - This is the actual number of patients on which the analysis was performed.

[158] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[159]
P-value	= 0.085
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.079

Notes:

[159] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[160]
P-value	= 0.502
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.056

Notes:

[160] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[161]
P-value	= 0.16
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.072

Notes:

[161] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment B vs treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[162]
P-value	= 0.285
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.065
upper limit	0.019

Notes:

[162] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[163]
P-value	= 0.735
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.035

Notes:

[163] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[164]
P-value	= 0.46
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.057

Notes:

[164] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Secondary: Change from baseline in peak FVC on Day 42

End point title	Change from baseline in peak FVC on Day 42

End point description:

The peak FVC is the maximum FVC value obtained between 15 minutes and 12 hours post-dose.
Post-dose FVC on Day 1 of each treatment period was recorded at 15'; 30'; 45'; 1h; 2h; 3h, 4h,6h, 8h, 11h30 and 12h post-study drug intake.
Baseline is the average of the FVC pre-dose measurements on Day 1 of each period (recorded at 45 and 10 minuted prior to study drug intake).

End point type	Secondary

End point timeframe:

On Day 42.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[165]	152[166]	153[167]	152[168]
Units: liters				
arithmetic mean (standard deviation)	0.395 (± 0.379)	0.456 (± 0.422)	0.423 (± 0.417)	0.373 (± 0.35)

Notes:

[165] - This is the actual number of patients on which the analysis was performed.

[166] - This is the actual number of patients on which the analysis was performed.

[167] - This is the actual number of patients on which the analysis was performed.

[168] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[169]
P-value	= 0.4
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.066

Notes:

[169] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[170]
P-value	= 0.043
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.092

Notes:

[170] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[171]
P-value	= 0.029
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.097

Notes:

[171] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=301 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority[172]
P-value	= 0.245
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.019
upper limit	0.073

Notes:

[172] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment C - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[173]
P-value	= 0.179
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.031

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.077

Notes:

[173] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an
innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[174]
P-value	= 0.859
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.05

Notes:

[174] - The peak FVC was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FVC (average of 45 and 10 minutes pre-dose FVC at Day 1) as covariate.

Secondary: Change from baseline in FVC at each time point post-dose on Day 1

End point title	Change from baseline in FVC at each time point post-dose on Day 1

End point description:

The baseline FVC is the mean of the pre-dose measurements recorded on Day 1 of each treatment period.
Post-dose FVC was recorded at 15’; 30’; 45’; 1h; 2h; 3h, 4h,6h, 8h, 11h30 and 12h post-study drug intake on Day 1.
Only change from baseline at the last timepoint (12h post-dose) on Day 1 is reported in the system. For the data on the other timepoints on the same day see pdf attached.

End point type	Secondary

End point timeframe:

On Day 1

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[175]	153[176]	156[177]	149[178]
Units: liters				
arithmetic mean (standard deviation)	0.098 (± 0.312)	0.086 (± 0.348)	0.098 (± 0.3)	0.075 (± 0.321)

Notes:

[175] - This is the actual number of patients on which the analysis was performed.

[176] - This is the actual number of patients on which the analysis was performed.

[177] - This is the actual number of patients on which the analysis was performed.

[178] - This is the actual number of patients on which the analysis was performed.

Attachments (see zip file)	FVC Change D1.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FVC at 2h post-dose on Day 14

End point title	Change from baseline in FVC at 2h post-dose on Day 14

End point description:

The baseline FVC is the mean of the pre-dose measurements recorded on Day 1 of each treatment period.
Post-dose FVC was recorded at 2h on Day 14.

End point type	Secondary

End point timeframe:

On Day 14

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	155[179]	155[180]	152[181]
Units: liters				
arithmetic mean (standard deviation)	0.278 (± 0.367)	0.318 (± 0.407)	0.254 (± 0.309)	0.225 (± 0.308)

Notes:

[179] - This is the actual number of patients on which the analysis was performed.

[180] - This is the actual number of patients on which the analysis was performed.

[181] - This is the actual number of patients on which the analysis was performed.

Attachments (see zip file)	FVC Change D14.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FVC at each time point post-dose on Day 42

End point title	Change from baseline in FVC at each time point post-dose on Day 42

End point description:

The baseline FVC is the mean of the pre-dose measurements recorded on Day 1 of each treatment period.
Post-dose FVC was recorded at 15'; 30'; 45'; 1h; 2h; 3h, 4h,6h, 8h, 11h30 and 12h post-study drug intake on Day 42.
Only change from baseline at the last timepoint (12h post-dose) on Day 42 is reported in the system. For the data on the other timepoints on the same day, please see the pdf attached.

End point type	Secondary

End point timeframe:

On Day 42.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	149[182]	150[183]	154[184]	152[185]
Units: liters				
arithmetic mean (standard deviation)	0.069 (± 0.399)	0.088 (± 0.395)	0.118 (± 0.421)	0.034 (± 0.347)

Notes:

[182] - This is the actual number of patients on which the analysis was performed.

[183] - This is the actual number of patients on which the analysis was performed.

[184] - This is the actual number of patients on which the analysis was performed.

[185] - This is the actual number of patients on which the analysis was performed.

Attachments (see zip file)	FVC Change D42.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Average total daily asthma symptoms, night-time

End point title	Average total daily asthma symptoms, night-time

End point description:

The average of daily asthma symptoms (morning/ evening) of a subgroup (Cough, Wheeze, Chest Tightness, Breathlessness) is the mean value of all morning/ evening measurements of that subgroup. Results on the average total daily asthma symptoms score (night-time) during the treatment period are presented for the ITT population.

End point type	Secondary

End point timeframe:

At visit 1 (Screening Visit) and at the first and third visit of each tratment period.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	154[186]	155[187]	151[188]
Units: score				
arithmetic mean (standard deviation)	2.111 (± 2.145)	1.998 (± 1.896)	2.181 (± 2.082)	1.974 (± 1.943)

Notes:

[186] - This is the actual number of patients on which the analysis was performed.

[187] - This is the actual number of patients on which the analysis was performed.

[188] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[189]
P-value	= 0.77
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.173
upper limit	0.128

Notes:

[189] - This secondary efficacy variables were analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[190]
P-value	= 0.682
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.181
upper limit	0.118

Notes:

[190] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[191]
P-value	= 0.85
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.164
upper limit	0.135

Notes:

[191] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[192]
P-value	= 0.909
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.158
upper limit	0.141

Notes:

[192] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[193]
P-value	= 0.915
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.141
upper limit	0.157

Notes:

[193] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment B - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[194]
P-value	= 0.825
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.132
upper limit	0.165

Notes:

[194] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Secondary: Average total daily asthma symptoms, day-time

End point title	Average total daily asthma symptoms, day-time

End point description:

The average of daily asthma symptoms (morning/ evening) of a subgroup (Cough, Wheeze, Chest Tightness, Breathlessness) is the mean value of all morning/ evening measurements of that subgroup. Results on the average total daily asthma symptoms score (day-time) during the treatment period are presented for the ITT population.

End point type	Secondary

End point timeframe:

At visit 1 (Screening Visit) and at the first and third visit of each tratment period.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	153[195]	155[196]	152[197]
Units: score				
arithmetic mean (standard deviation)	2.384 (± 2.056)	2.3 (± 1.905)	2.472 (± 2.098)	2.215 (± 1.908)

Notes:

[195] - This is the actual number of patients on which the analysis was performed.

[196] - This is the actual number of patients on which the analysis was performed.

[197] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[198]
P-value	= 0.917
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.165
upper limit	0.148

Notes:

[198] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[199]
P-value	= 0.792
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.134
upper limit	0.176

Notes:

[199] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[200]
P-value	= 0.656
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.19

Notes:

[200] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[201]
P-value	= 0.713
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.127
upper limit	0.185

Notes:

[201] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[202]
P-value	= 0.582
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.112
upper limit	0.199

Notes:

[202] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=308 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment B - ITT population
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority[203]
P-value	= 0.855
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.169

Notes:

[203] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Secondary: Percentage of asthma control days

End point title	Percentage of asthma control days

End point description:

The percentage is calculated as the number of asthma control days / number of days with available data.

End point type	Secondary

End point timeframe:

Measured between the first and the third visit of each treatment period.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	154[204]	155[205]	152[206]
Units: percent				
arithmetic mean (standard deviation)	25.7 (± 33.1)	27.3 (± 34.5)	25.1 (± 34.1)	26.6 (± 34.2)

Notes:

[204] - This is the actual number of patients on which the analysis was performed.

[205] - This is the actual number of patients on which the analysis was performed.

[206] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[207]
P-value	= 0.481
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	4.8

Notes:

[207] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment D - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[208]
P-value	= 0.484
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	4.8

Notes:

[208] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment D - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[209]
P-value	= 0.562
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	4.6

Notes:

[209] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[210]
P-value	= 0.99
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	3.5

Notes:

[210] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment A - ITT population

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[211]
P-value	= 0.896
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	3.3

Notes:

[211] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment C - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[212]
P-value	= 0.906
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	3.3

Notes:

[212] - This secondary efficacy variable was analysed on the ITT population using an analysis of variance (ANOVA) model including treatment, period and patient as fixed effects.

Secondary: Average use of rescue medication (number of puffs/day)

End point title	Average use of rescue medication (number of puffs/day)

End point description:

The average use of rescue medication (number of puffs per day) is determined as the total number of puffs of rescue mediation taken / number of days with available data.

End point type	Secondary

End point timeframe:

Daily during run-in/wash-out & treatment periods.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	154[213]	155[214]	152[215]
Units: number of puffs/ day				
arithmetic mean (standard deviation)	0.9 (± 1.3)	0.8 (± 1.3)	0.9 (± 1.5)	0.8 (± 1.5)

Notes:

[213] - This is the actual number of patients on which the analysis was performed.

[214] - This is the actual number of patients on which the analysis was performed.

[215] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[216]
P-value	= 0.55
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[216] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment D - ITT population v Treatment B - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[217]
P-value	= 0.883
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[217] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment D - ITT population v Treatment C - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[218]
P-value	= 0.325
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[218] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[219]
P-value	= 0.649
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[219] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment C - ITT population

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[220]
P-value	= 0.701
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[220] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment B - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[221]
P-value	= 0.4
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Notes:

[221] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Secondary: Average use of rescue medication (number of times/day)

End point title	Average use of rescue medication (number of times/day)

End point description:

The average use of rescue medication (number of times per day) is determined as the total number of times of rescue medication taken/ number of days with available data.

End point type	Secondary

End point timeframe:

Daily during run-in/wash-out & treatment periods.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	154[222]	155[223]	152[224]
Units: number of times/ day				
arithmetic mean (standard deviation)	0.7 (± 1)	0.6 (± 0.9)	0.6 (± 1)	0.6 (± 0.9)

Notes:

[222] - This is the actual number of patients on which the analysis was performed.

[223] - This is the actual number of patients on which the analysis was performed.

[224] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=304 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority[225]
P-value	= 0.95
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[225] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment D - ITT population v Treatment B - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[226]
P-value	= 0.744
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[226] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment D - ITT population v Treatment C - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[227]
P-value	= 0.629
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[227] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=306 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment B - ITT population
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[228]
P-value	= 0.793
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[228] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment C - ITT population

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[229]
P-value	= 0.674
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[229] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=309 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment B - ITT population
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority[230]
P-value	= 0.875
Method	ANOVA
Parameter estimate	adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.1

Notes:

[230] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects, without multiplicity adjustments.

Secondary: Change from baseline in ACQ total score on Day 42

End point title	Change from baseline in ACQ total score on Day 42

End point description:

Baseline is the calculated Asthma Control Questionnaire (ACQ) score of Day 1 of the respective treatment period.

End point type	Secondary

End point timeframe:

On Day 42.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Treatment D - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[231]	153[232]	155[233]	152[234]
Units: score				
arithmetic mean (standard deviation)	-0.126 (± 0.599)	-0.246 (± 0.689)	-0.207 (± 0.676)	-0.193 (± 0.552)

Notes:

[231] - This is the actual number of patients on which the analysis was performed.

[232] - This is the actual number of patients on which the analysis was performed.

[233] - This is the actual number of patients on which the analysis was performed.

[234] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=302 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment D - ITT population
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[235]
P-value	= 0.835
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.116
upper limit	0.093

Notes:

[235] - The change from baseline in ACQ total score on Day 42 was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline ACQ total score as covariate. No multiplicity adjustments are done.

Statistical analysis title	Treatment B vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment D - ITT population v Treatment B - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[236]
P-value	= 0.583
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.029

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.132
upper limit	0.074

Notes:

[236] - The change from baseline in ACQ total score on Day 42 was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline ACQ total score as covariate. No multiplicity adjustments are done.

Statistical analysis title	Treatment C vs Treatment D

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=307 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment D - ITT population v Treatment C - ITT population
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[237]
P-value	= 0.727
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.122
upper limit	0.085

Notes:

[237] - The change from baseline in ACQ total score on Day 42 was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline ACQ total score as covariate. No multiplicity adjustments are done.

Statistical analysis title	Treatment B vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=303 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment B - ITT population v Treatment A - ITT population
Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority[238]
P-value	= 0.737
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.122
upper limit	0.086

Notes:

[238] - The change from baseline in ACQ total score on Day 42 was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline ACQ total score as covariate. No multiplicity adjustments are done.

Statistical analysis title	Treatment C vs Treatment A

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=305 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment A - ITT population v Treatment C - ITT population
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[239]
P-value	= 0.89
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.111
upper limit	0.086

Notes:

[239] - The change from baseline in ACQ total score on Day 42 was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline ACQ total score as covariate. No multiplicity adjustments are done.

Statistical analysis title	Treatment C vs Treatment B

Statistical analysis description:

In a cross-over study, groups examined should not be added. The number N=308 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Treatment C - ITT population v Treatment B - ITT population
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority[240]
P-value	= 0.841
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.093
upper limit	0.114

Notes:

[240] - The change from baseline in ACQ total score on Day 42 was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline ACQ total score as covariate. No multiplicity adjustments are done.

Secondary: SBP change from baseline on Day 14

End point title	SBP change from baseline on Day 14

End point description:

Baseline is the pre-dose measurement on Day 1 in each treatment period.

End point type	Secondary

End point timeframe:
On Day 14

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152	155[241]	155[242]	152[243]
Units: mmHg				
arithmetic mean (standard deviation)	-0.7 (± 11.4)	1.9 (± 9.9)	-0.7 (± 9.5)	-0.7 (± 10.2)

Notes:
[241] - This is the actual number of patients on which the analysis was performed.
[242] - This is the actual number of patients on which the analysis was performed.
[243] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: HR change from baseline post-dose on Day 1

End point title	HR change from baseline post-dose on Day 1

End point description:
Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period. Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:
On Day 1

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146[244]	153[245]	156[246]	151[247]
Units: bpm				
arithmetic mean (standard deviation)	-1 (± 6)	-2.1 (± 5.3)	-1.9 (± 6.6)	-1.6 (± 5.3)

Notes:
[244] - This is the actual number of patients on which the analysis was performed.
[245] - This is the actual number of patients on which the analysis was performed.
[246] - This is the actual number of patients on which the analysis was performed.
[247] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: PR change from baseline post-dose on Day 1

End point title	PR change from baseline post-dose on Day 1

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On Day 1

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146[248]	153[249]	156[250]	151[251]
Units: ms				
arithmetic mean (standard deviation)	-1.2 (± 7.3)	-0.5 (± 8.2)	-0.1 (± 9.4)	0.3 (± 7.4)

Notes:

[248] - This is the actual number of patients on which the analysis was performed.

[249] - This is the actual number of patients on which the analysis was performed.

[250] - This is the actual number of patients on which the analysis was performed.

[251] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: QRS change from baseline post-dose on Day 1

End point title	QRS change from baseline post-dose on Day 1

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On Day 1

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146[252]	153[253]	156[254]	151[255]
Units: ms				
arithmetic mean (standard deviation)	0.7 (± 4.1)	0.7 (± 5.2)	-0.5 (± 4.3)	0.5 (± 4.5)

Notes:

[252] - This is the actual number of patients on which the analysis was performed.

[253] - This is the actual number of patients on which the analysis was performed.

[254] - This is the actual number of patients on which the analysis was performed.

[255] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: QTcF change from baseline post-dose on Day 1

End point title	QTcF change from baseline post-dose on Day 1

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On Day 1

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146[256]	153[257]	156[258]	151[259]
Units: ms				
arithmetic mean (standard deviation)	3.1 (± 9.4)	1.3 (± 8.9)	1.3 (± 9.8)	2.1 (± 8.3)

Notes:

[256] - This is the actual number of patients on which the analysis was performed.

[257] - This is the actual number of patients on which the analysis was performed.

[258] - This is the actual number of patients on which the analysis was performed.

[259] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: SBP change from baseline on Day 42

End point title	SBP change from baseline on Day 42

End point description:

Baseline is the pre-dose measurement on Day 1 in each treatment period.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[260]	153[261]	155[262]	152[263]
Units: mmHg				
arithmetic mean (standard deviation)	-0.5 (± 11.2)	2.4 (± 10.3)	1.3 (± 10.2)	-1.5 (± 9.6)

Notes:
[260] - This is the actual number of patients on which the analysis was performed.
[261] - This is the actual number of patients on which the analysis was performed.
[262] - This is the actual number of patients on which the analysis was performed.
[263] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: DBP change from baseline on Day 14

End point title	DBP change from baseline on Day 14

End point description:
Baseline is the pre-dose measurement on Day 1 in each treatment period.

End point type	Secondary

End point timeframe:
On Day 14

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	152[264]	155[265]	155[266]	152[267]
Units: mmHg				
arithmetic mean (standard deviation)	-0.3 (± 7.4)	1.4 (± 6.6)	0.3 (± 7.7)	-0.1 (± 8.5)

Notes:
[264] - This is the actual number of patients on which the analysis was performed.
[265] - This is the actual number of patients on which the analysis was performed.
[266] - This is the actual number of patients on which the analysis was performed.
[267] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: DBP change from baseline on Day 42

End point title	DBP change from baseline on Day 42

End point description:
Baseline is the pre-dose measurement on Day 1 in each treatment period.

End point type	Secondary

End point timeframe:
On day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	150[268]	153[269]	155[270]	152[271]
Units: mmHg				
arithmetic mean (standard deviation)	-0.4 (± 6.6)	1.2 (± 7.3)	0.1 (± 7.8)	-0.6 (± 7.5)

Notes:

[268] - This is the actual number of patients on which the analysis was performed.

[269] - This is the actual number of patients on which the analysis was performed.

[270] - This is the actual number of patients on which the analysis was performed.

[271] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: QTcF change from baseline pre-dose on Day 42

End point title	QTcF change from baseline pre-dose on Day 42

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[272]	151[273]	153[274]	150[275]
Units: ms				
arithmetic mean (standard deviation)	-0.3 (± 11.9)	-2.3 (± 13.9)	-2.1 (± 12.3)	0.9 (± 11.9)

Notes:

[272] - This is the actual number of patients on which the analysis was performed.

[273] - This is the actual number of patients on which the analysis was performed.

[274] - This is the actual number of patients on which the analysis was performed.

[275] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: QTcF change from baseline post-dose on Day 42

End point title	QTcF change from baseline post-dose on Day 42

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:
On Day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[276]	151[277]	151[278]	150[279]
Units: ms				
arithmetic mean (standard deviation)	1.6 (± 12.2)	1.2 (± 13.4)	1.1 (± 11.6)	2.9 (± 12.8)

Notes:
[276] - This is the actual number of patients on which the analysis was performed.
[277] - This is the actual number of patients on which the analysis was performed.
[278] - This is the actual number of patients on which the analysis was performed.
[279] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: HR change from baseline pre-dose on Day 42

End point title	HR change from baseline pre-dose on Day 42

End point description:
Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:
On Day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[280]	151[281]	153[282]	150[283]
Units: bpm				
arithmetic mean (standard deviation)	-0.8 (± 7.5)	-0.4 (± 9)	0.3 (± 8.7)	-0.1 (± 8)

Notes:
[280] - This is the actual number of patients on which the analysis was performed.
[281] - This is the actual number of patients on which the analysis was performed.
[282] - This is the actual number of patients on which the analysis was performed.
[283] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: HR change from baseline post-dose on Day 42

End point title	HR change from baseline post-dose on Day 42

End point description:

Baseline is the average of the 3 individual pre-dose values on Day1 in each treatment period. Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[284]	151[285]	151[286]	150[287]
Units: bpm				
arithmetic mean (standard deviation)	-1.9 (± 7.6)	-1.8 (± 8.7)	-1.5 (± 9.2)	-2.2 (± 8.4)

Notes:

[284] - This is the actual number of patients on which the analysis was performed.

[285] - This is the actual number of patients on which the analysis was performed.

[286] - This is the actual number of patients on which the analysis was performed.

[287] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: PR change from baseline pre-dose on Day 42

End point title	PR change from baseline pre-dose on Day 42

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period. Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[288]	151[289]	153[290]	150[291]
Units: ms				
arithmetic mean (standard deviation)	-0.9 (± 10.1)	-1.4 (± 11.8)	-1.5 (± 12.6)	0.5 (± 10.1)

Notes:

[288] - This is the actual number of patients on which the analysis was performed.

[289] - This is the actual number of patients on which the analysis was performed.

[290] - This is the actual number of patients on which the analysis was performed.

[291] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: PR change from baseline post-dose on Day 42

End point title	PR change from baseline post-dose on Day 42

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[292]	151[293]	151[294]	150[295]
Units: ms				
arithmetic mean (standard deviation)	-1.3 (± 9.8)	-1.4 (± 11.4)	-0.8 (± 14)	-0.1 (± 10.4)

Notes:

[292] - This is the actual number of patients on which the analysis was performed.

[293] - This is the actual number of patients on which the analysis was performed.

[294] - This is the actual number of patients on which the analysis was performed.

[295] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: QRS change from baseline pre-dose on Day 42

End point title	QRS change from baseline pre-dose on Day 42

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[296]	151[297]	153[298]	150[299]
Units: ms				
arithmetic mean (standard deviation)	0.7 (± 6.3)	-0.7 (± 5.4)	-0.9 (± 6.1)	0.8 (± 6.2)

Notes:

[296] - This is the actual number of patients on which the analysis was performed.

[297] - This is the actual number of patients on which the analysis was performed.

[298] - This is the actual number of patients on which the analysis was performed.

[299] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Secondary: QRS change from baseline post-dose on Day 42

End point title	QRS change from baseline post-dose on Day 42

End point description:

Baseline is the average of the 3 individual pre-dose values on Day 1 in each treatment period.
Patients with a pacemaker are excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm are also excluded.

End point type	Secondary

End point timeframe:

On Day 42

End point values	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population	Treatment D - safety population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	145[300]	151[301]	151[302]	150[303]
Units: ms				
arithmetic mean (standard deviation)	0.7 (± 6.1)	0.8 (± 5.4)	-0.5 (± 5.6)	0.7 (± 6.6)

Notes:

[300] - This is the actual number of patients on which the analysis was performed.

[301] - This is the actual number of patients on which the analysis was performed.

[302] - This is the actual number of patients on which the analysis was performed.

[303] - This is the actual number of patients on which the analysis was performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
At each visit from Visit 1 (Screening) to Visit 10 and, afterwards, to follow-up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Treatment A - safety population
Reporting group description: -	
Reporting group title	Treatment B - safety population
Reporting group description: -	
Reporting group title	Treatment C - safety population
Reporting group description: -	
Reporting group title	Treatment D - safety population
Reporting group description: -	

Serious adverse events	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 152 (0.66%)	1 / 156 (0.64%)	1 / 157 (0.64%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment D - safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 153 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery stenosis			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 152 (13.16%)	19 / 156 (12.18%)	13 / 157 (8.28%)
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 152 (1.32%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 152 (0.66%)	4 / 156 (2.56%)	1 / 157 (0.64%)
occurrences (all)	1	4	1
Cough			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	0 / 152 (0.00%)	2 / 156 (1.28%)	0 / 157 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 152 (0.66%)	1 / 156 (0.64%)	1 / 157 (0.64%)
occurrences (all)	1	1	1
Transaminases increased			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	1 / 157 (0.64%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Joint injury			

subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	1 / 157 (0.64%)
occurrences (all)	0	0	1
Soft tissue injury			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Myocardial ischaemia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 152 (2.63%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	4	1	0
Tremor			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	1 / 157 (0.64%)
occurrences (all)	0	0	1
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	1 / 157 (0.64%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	1 / 157 (0.64%)
occurrences (all)	0	0	1
Toothache			

subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 152 (1.32%)	5 / 156 (3.21%)	3 / 157 (1.91%)
occurrences (all)	2	5	3
Pharyngitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	3 / 157 (1.91%)
occurrences (all)	0	0	3
Rhinitis			
subjects affected / exposed	2 / 152 (1.32%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	2	0	0
Acute tonsilitis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	1 / 157 (0.64%)
occurrences (all)	0	0	1

Cystitis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	1 / 157 (0.64%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	1 / 157 (0.64%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Pharyngitis bacterial			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0
Tracheitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Vulvovaginitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 156 (0.00%)	0 / 157 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	1 / 157 (0.64%)
occurrences (all)	0	1	1
Dyslipidaemia			
subjects affected / exposed	0 / 152 (0.00%)	1 / 156 (0.64%)	0 / 157 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Treatment D - safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 153 (9.15%)		
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Hypertension			

subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	6 / 153 (3.92%)		
occurrences (all)	7		
Cough			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Transaminases increased			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	1 / 153 (0.65%) 1		
Joint injury subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Soft tissue injury subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Sunburn subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Cardiac disorders Bundle branch block right subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Myocardial ischaemia subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Tremor subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Eye disorders Dry eye subjects affected / exposed occurrences (all)	1 / 153 (0.65%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Dry mouth subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		

Nausea subjects affected / exposed occurrences (all) Toothache subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0 0 / 153 (0.00%) 0 0 / 153 (0.00%) 0		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Renal and urinary disorders Calculus urinary subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	0 / 153 (0.00%) 0 0 / 153 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Acute tonsilitis	2 / 153 (1.31%) 2 0 / 153 (0.00%) 0 0 / 153 (0.00%) 0		

subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Gastrointestinal viral infection			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Gingivitis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences (all)	1		
Pharyngitis bacterial			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		
Tracheitis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences (all)	1		
Vulvovaginitis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences (all)	1		
Dyslipidaemia			
subjects affected / exposed	0 / 153 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There are no limitations or caveats to this summary of results.

Notes: