



Clinical trial results:

A MULTICENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 2-WAY CROSS-OVER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CHF 5259 (GLYCOPYRROLATE BROMIDE) pMDI ON TOP OF QVAR® pMDI FOR THE TREATMENT OF PATIENTS WITH UNCONTROLLED ASTHMA ON LOW-MEDIUM DOSE OF INHALED CORTICOSTEROIDS

Summary

EudraCT number	2014-001442-16
Trial protocol	DE IT PL BG NL
Global end of trial date	13 August 2015

Results information

Result version number	v1 (current)
This version publication date	14 August 2016
First version publication date	14 August 2016

Trial information

Trial identification

Sponsor protocol code	CCD-05993AB1-02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02296411
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, +39 05212791, ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A, +39 05212791, ClinicalTrials_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	13 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 August 2015
Global end of trial reached?	Yes
Global end of trial date	13 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the superiority of CHF 5259 pMDI (glycopyrrolate bromide) (50 µg total daily dose) versus placebo 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:

At Screening visit (V1), all eligible patients had to switch to an ICS monotherapy at a clinical dose comparable to their previous treatment.

Background medication: Qvar® pMDI 50 µg or 100 µg.

Dose: Qvar® pMDI 50 µg or 100 µg b.i.d., total daily dose of Qvar® pMDI ranged from 100 µg to 400 µg.

Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.

Evidence for comparator: -

Actual start date of recruitment	21 November 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	Netherlands: 1
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Bulgaria: 37
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	89
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multinational study was conducted at 28 sites (24 active) in 5 countries: Bulgaria, Germany, Italy, The Netherlands and Poland.

Pre-assignment

Screening details:

A total of 138 patients were screened, 98 patients were randomised and 97 (99.0%) 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

Blinding implementation details:

The randomisation list was provided to the labelling facility but was not available to patients, Investigators, monitors or employees of the centre 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 as they did not have direct access to the randomisation list.

Arms

Are arms mutually exclusive?	Yes
Arm title	CHF5259 pMDI - placebo pMDI

Arm description:

Two puffs of CHF 5259 pMDI 12.5 µg twice a day (b.i.d.), total daily dose of CHF 5259 pMDI was 50 µg.

Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.

Two puffs of matched placebo of CHF 5259 pMDI b.i.d.

Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.

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

Dosage and administration details:

Two puffs of CHF 5259 12.5 µg b.i.d.

Investigational medicinal product name	Placebo pMDI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Dose: two puffs b.i.d.

Arm title	Placebo pMDI - CHF 5259 pMDI
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Arm description:

Two puffs of matched placebo of CHF 5259 pMDI b.i.d.

Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.

Two puffs of CHF 5259 pMDI 12.5 µg twice a day (b.i.d.), total daily dose of CHF 5259 pMDI was 50 µg.

Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.

Arm type	Experimental
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Investigational medicinal product name	CHF 5259 pMDI
Investigational medicinal product code	
Other name	Glycopirrolate bromide
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Two puffs of CHF 5259 12.5 µg b.i.d.	
Investigational medicinal product name	Placebo pMDI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
Two puffs of matched placebo of CHF 5259 pMDI b.i.d.	

Number of subjects in period 1	CHF5259 pMDI - placebo pMDI	Placebo pMDI - CHF 5259 pMDI
Started	50	48
Completed	50	47
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups

Reporting group title	CHF5259 pMDI - placebo pMDI
Reporting group description:	
Two puffs of CHF 5259 pMDI 12.5 µg twice a day (b.i.d.), total daily dose of CHF 5259 pMDI was 50 µg. Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.	
Two puffs of matched placebo of CHF 5259 pMDI b.i.d. Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.	
Reporting group title	Placebo pMDI - CHF 5259 pMDI
Reporting group description:	
Two puffs of matched placebo of CHF 5259 pMDI b.i.d. Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.	
Two puffs of CHF 5259 pMDI 12.5 µg twice a day (b.i.d.), total daily dose of CHF 5259 pMDI was 50 µg. Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.	

Reporting group values	CHF5259 pMDI - placebo pMDI	Placebo pMDI - CHF 5259 pMDI	Total
Number of subjects	50	48	98
Age categorical			
Units: Subjects			
Adults (18-64 years)	45	44	89
From 65-84 years	5	4	9
Age continuous			
Units: years			
arithmetic mean	48.8	47.2	
standard deviation	± 14	± 12.8	-
Gender categorical			
Units: Subjects			
Female	30	31	61
Male	20	17	37

End points

End points reporting groups

Reporting group title	CHF5259 pMDI - placebo pMDI
Reporting group description: Two puffs of CHF 5259 pMDI 12.5 µg twice a day (b.i.d.), total daily dose of CHF 5259 pMDI was 50 µg. Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator. Two puffs of matched placebo of CHF 5259 pMDI b.i.d. Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.	
Reporting group title	Placebo pMDI - CHF 5259 pMDI
Reporting group description: Two puffs of matched placebo of CHF 5259 pMDI b.i.d. Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator. Two puffs of CHF 5259 pMDI 12.5 µg twice a day (b.i.d.), total daily dose of CHF 5259 pMDI was 50 µg. Mode of administration: Metered dose inhalation of pressurised solution using a standard actuator.	
Subject analysis set title	CHF5259 pMDI - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after baseline;	
Subject analysis set title	Placebo pMDI - ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: all randomised patients who received at least one dose of the study medication and with at least one available evaluation of efficacy after baseline;	
Subject analysis set title	CHF5259 pMDI - safety population
Subject analysis set type	Safety analysis
Subject analysis set description: all randomised patients who received at least one dose of the study medication.	
Subject analysis set title	Placebo pMDI - safety population
Subject analysis set type	Safety analysis
Subject analysis set description: All randomised patients who received at least one dose of the study medication.	
Subject analysis set title	CHF5259 pMDI - PP population
Subject analysis set type	Per protocol
Subject analysis set description: Per-Protocol (PP) population: all patients from the ITT population without any major protocol deviations	
Subject analysis set title	Placebo pMDI - PP population
Subject analysis set type	Per protocol
Subject analysis set description: Per-Protocol (PP) population: all patients from the ITT population without any major protocol deviations	

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

End point title	FEV1 AUC0-12h normalized by time on Day 42
End point description: AUC0-12h = area under the curve between time 0 and 12 hours; FEV1 was measured at 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 11.5h and 12h post-dose.	
End point type	Primary
End point timeframe: On day 42	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population	CHF5259 pMDI - PP population	Placebo pMDI - PP population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	95 ^[1]	96 ^[2]	86 ^[3]	82 ^[4]
Units: Liter				
arithmetic mean (standard deviation)	2.47 (± 0.857)	2.373 (± 0.83)	2.48 (± 0.849)	2.365 (± 0.827)

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	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=191 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Placebo pMDI - ITT population v CHF5259 pMDI - ITT population
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.092
upper limit	0.177

Notes:

[5] - The FEV1 AUC0-12h normalised by time on Day 42 was analysed using an analysis of covariance (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.

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=168 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	CHF5259 pMDI - PP population v Placebo pMDI - PP population
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.128

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.082
upper limit	0.174

Notes:

[6] - The FEV1 AUC0-12h normalised by time on Day 42 was analysed using an analysis of covariance (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.

Secondary: Change from baseline in peak FEV1 at Day 42

End point title	Change from baseline in peak FEV1 at Day 42
End point description:	
The peak FEV1 is determined as the maximum FEV1 value obtained between 15 minutes and 12 hours post-dose. The baseline value is the mean of the pre-dose measurement of FEV1 at Day 1 of each treatment period.	
End point type	Secondary
End point timeframe:	
On Day 42	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population	CHF5259 pMDI - PP population	Placebo pMDI - PP population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	97 ^[7]	97 ^[8]	91 ^[9]	89 ^[10]
Units: Liter				
arithmetic mean (standard deviation)	0.394 (± 0.281)	0.278 (± 0.293)	0.392 (± 0.263)	0.258 (± 0.299)

Notes:

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

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

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.137

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.18

Notes:

[11] - The change from baseline in peak FEV1 on Day 42 was analysed using an analysis of covariance (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.

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
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Statistical analysis description:

In a Cross-over study, groups examined should not be added up. The number N=180 (subject analysis set) is an innate error of the EudraCT database system

Comparison groups	CHF5259 pMDI - PP population v Placebo pMDI - PP population
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.144
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.098
upper limit	0.191

Notes:

[12] - The change from baseline in peak FEV1 on Day 42 was analysed using an analysis of covariance (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.

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

End point title	FEV1 AUC0-12h normalized by time on Day 1
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End point description:

FEV1 AUC0-12h = Area Under the Curve between time 0 and 12 hours.

FEV1 was measured at 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 11.5h and 12h post-dose.

End point type	Secondary
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End point timeframe:

On day 1

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[13]	96 ^[14]		
Units: Liter				
arithmetic mean (standard deviation)	2.482 (± 0.862)	2.356 (± 0.835)		

Notes:

[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	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=193 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.155

Notes:

[15] - The FEV1 AUC0-12h normalised by time on Day 1 was analysed using an analysis of covariance (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.

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.	
FEV1 was measured at 15 min, 30 min, 45 min, 1h, 2h, 3h.	
End point type	Secondary
End point timeframe:	
On day 1	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[16]	97 ^[17]		
Units: Liters				
arithmetic mean (standard deviation)	2.496 (± 0.863)	2.344 (± 0.815)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
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Statistical analysis description:

In a Cross-over study, groups examined should not be added up. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.187

Notes:

[18] - The FEV1 AUC0-3h normalised by time on Day 1 was analysed using an analysis of covariance (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.

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

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

AUC0-3h Area Under the Curve between time 0 and 3 hours.
FEV1 was measured at 15 min, 30 min, 45 min, 1h, 2h, 3h.

End point type	Secondary
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End point timeframe:

On Day 42

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96 ^[19]	97 ^[20]		
Units: Liters				
arithmetic mean (standard deviation)	2.498 (± 0.87)	2.357 (± 0.839)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=193 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.101
upper limit	0.201

Notes:

[21] - The FEV1 AUC0-3h normalised by time on Day 42 was analysed using an analysis of covariance (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.

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 determined as the maximum FEV1 value obtained between 15 minutes and 12 hours post-dose. The baseline value is the mean of the pre-dose measurement of FEV1 at Day 1 of each treatment period.	
End point type	Secondary
End point timeframe:	
On day 1	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[22]	97 ^[23]		
Units: Liters				
arithmetic mean (standard deviation)	0.384 (± 0.248)	0.286 (± 0.237)		

Notes:

[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.

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description: In a Cross-over study, groups examined should not be added up. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[24]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.071
upper limit	0.154

Notes:

[24] - The peak FEV1 on Day 1 was analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FEV1 (mean of the pre-dose measurements of FEV1 at Day 1) as a covariate.

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

End point title	Change from baseline in pre-dose morning through FEV1 on Day 42
End point description: The pre-dose morning FEV1 is defined as the mean of the two measurements at 45 and 15 minutes pre-dose.	
End point type	Secondary
End point timeframe: On Day 42	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[25]	97 ^[26]		
Units: liters				
arithmetic mean (standard deviation)	0.136 (± 0.291)	0.041 (± 0.258)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
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Statistical analysis description:

In a Cross-over study, groups examined should not be added up. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.164

Notes:

[27] - The changes from baseline in pre-dose morning FEV1 were analysed by means of an ANCOVA model with treatment, patient and period as fixed effects and baseline FEV1 (mean of the pre-dose measurements of FEV1 at Day 1) as a covariate.

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

End point title	Change from baseline in ACQ total score at Day 42
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End point description:

ACQ = Asthma Control Questionnaire.

The ACQ total score is the sum of the 7 ACQ scores.

End point type	Secondary
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End point timeframe:

On Day 42

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[28]	97 ^[29]		
Units: Number				
arithmetic mean (standard deviation)	-0.39 (± 0.59)	-0.17 (± 0.56)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
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Statistical analysis description:

In a Cross-over study, groups examined should not be added up. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[30]
P-value	= 0.026
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.02

Notes:

[30] - 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 a covariate. Baseline is the calculated Asthma Control Questionnaire (ACQ) score of Day 1 of the respective treatment period.

Secondary: Average daily morning PEF

End point title	Average daily morning PEF
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End point description:

The average daily morning PEF is the mean value of all morning PEF measurements.

End point type	Secondary
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End point timeframe:

Daily during run-in and treatment periods.

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96 ^[31]	97 ^[32]		
Units: liters/ min				
arithmetic mean (standard deviation)	363.2 (± 117.7)	346.9 (± 111.5)		

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.

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=193 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Placebo pMDI - ITT population v CHF5259 pMDI - ITT population
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	< 0.001
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	14.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.8
upper limit	20.6

Notes:

[33] - The average morning PEFs were analysed by means of an ANOVA model with treatment, patient and period as fixed effects.

Secondary: Average daily evening PEF

End point title	Average daily evening PEF
End point description:	
The average daily evening PEF is the mean value of all evening PEF measurements. It is set to missing when there are less than 20 non-missing values	
End point type	Secondary
End point timeframe:	
Daily during run-in and treatment periods.	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96 ^[34]	97 ^[35]		
Units: liters/min				
arithmetic mean (standard deviation)	372.4 (± 117)	355.5 (± 110.5)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
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Statistical analysis description:

In a Cross-over study, groups examined should not be added up. The number N=193 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority ^[36]
P-value	< 0.001
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.3
upper limit	21

Notes:

[36] - The average evening PEFs were analysed by means of an ANOVA model with treatment, patient and period as fixed effects.

Secondary: Average daily asthma symptoms, day-time

End point title	Average daily asthma symptoms, day-time
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End point description:

The average of daily asthma symptoms (daytime) of a symptom (Cough, Wheeze, Chest Tightness, Breathlessness) is the mean value of all daytime measurements of that symptom. If there are less than 20 non-missing values, the average is considered missing.

End point type	Secondary
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End point timeframe:

Daily during run-in and treatment periods.

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96 ^[37]	97 ^[38]		
Units: number				
arithmetic mean (standard deviation)	2.62 (± 1.98)	2.66 (± 1.84)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
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Statistical analysis description:

In a Cross-over study, groups examined should not be added up. The number N=193 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority ^[39]
P-value	= 0.608
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.21
upper limit	0.12

Notes:

[39] - The average daily morning Asthma Symptom Scores were analysed by means of an ANOVA model with treatment, patient and period as fixed effects.

Secondary: Average daily asthma symptoms, night-time

End point title	Average daily asthma symptoms, night-time
End point description:	
The average of daily asthma symptoms (nighttime) of a symptom (Cough, Wheeze, Chest Tightness, Breathlessness) is the mean value of all nighttime measurements of that symptom. If there are less than 20 non-missing values, the average is considered missing.	
End point type	Secondary
End point timeframe:	
Daily during run-in and treatment periods.	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96 ^[40]	97 ^[41]		
Units: number				
arithmetic mean (standard deviation)	2.35 (± 2.1)	2.39 (± 2)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=193 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority ^[42]
P-value	= 0.435
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.1

Notes:

[42] - The average daily evening Asthma Symptom Scores were analysed by means of an ANOVA model with treatment, patient and period 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 medication taken / number of days with available data.	
End point type	Secondary
End point timeframe:	
Daily during run-in and treatment periods.	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[43]	97 ^[44]		
Units: number of puffs/ day				
arithmetic mean (standard deviation)	1 (± 1.6)	1.1 (± 1.5)		

Notes:

[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	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[45]
P-value	= 0.462
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:

[45] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects.

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 and treatment periods.	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[46]	97 ^[47]		
Units: times/ day				
arithmetic mean (standard deviation)	0.8 (± 1.4)	0.9 (± 1.3)		

Notes:

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

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

Statistical analyses

Statistical analysis title	CHF5259 pMDI vs Placebo pMDI
Statistical analysis description:	
In a Cross-over study, groups examined should not be added up. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[48]
P-value	= 0.379
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0

Notes:

[48] - The average use of rescue medication was analysed by means of an ANOVA model with treatment, patient and period as fixed effects.

Secondary: Change from baseline in FEV1 percentage of predicted normal value on Day 1

End point title	Change from baseline in FEV1 percentage of predicted normal value on Day 1
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End point description:

FEV1 was measured at 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 11.5h and 12h post-dose. The baseline value is the mean of the pre-dose measurement of FEV1 at Day 1 of each treatment period.

Only changes from baseline at 12h post-dose data are reported. For the changes from baseline of other time points, please see the attached file.

End point type	Secondary
End point timeframe:	
On day 1	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[49]	97 ^[50]		
Units: percentage				
arithmetic mean (standard deviation)	5.1 (± 8.1)	2.9 (± 7.5)		

Notes:

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

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

Attachments (see zip file)	FEV1 Day 1 Change from Baseline.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FEV1 percentage of predicted normal value on Day 42

End point title	Change from baseline in FEV1 percentage of predicted normal value on Day 42
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End point description:

FEV1 was measured at 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 11.5h and 12h post-dose. The baseline value is the mean of the pre-dose measurement of FEV1 at Day 1 of each treatment period.

Only changes from baseline at 12h post-dose data are reported. For the changes from baseline of other time points, please see the attached file.

End point type	Secondary
End point timeframe:	
On Day 42	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[51]	96 ^[52]		
Units: percentage				
arithmetic mean (standard deviation)	5.8 (± 8.9)	2.9 (± 8.5)		

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.

Attachments (see zip file)	FEV1 Day 42 Change from Baseline.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FVC on Day 1

End point title	Change from baseline in FVC on Day 1
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End point description:

FVC was measured at 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 11.5h and 12h post-dose. The baseline value is the mean of the pre-dose measurement of FVC at Day 1 of each treatment period. Only changes from baseline at 12h post-dose data are reported. For the changes from baseline of other time points, please see the attached file.

End point type	Secondary
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End point timeframe:

On Day 1

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[53]	97 ^[54]		
Units: Liters				
arithmetic mean (standard deviation)	0.105 (± 0.348)	0.114 (± 0.319)		

Notes:

[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.

Attachments (see zip file)	FVC Day 1 Change from Baseline.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FVC on Day 42

End point title	Change from baseline in FVC on Day 42
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End point description:

FVC was measured at 15 min, 30 min, 45 min, 1h, 2h, 3h, 4h, 6h, 8h, 11.5h and 12h post-dose.

The baseline value is the mean of the pre-dose measurement of FVC at Day 1 of each treatment period. Only changes from baseline at 12h post-dose data are reported. For the changes from baseline of other time points, please see the attached file.

End point type	Secondary
End point timeframe:	
On day 42	

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[55]	96 ^[56]		
Units: liters				
arithmetic mean (standard deviation)	0.096 (± 0.34)	0.068 (± 0.346)		

Notes:

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

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

Attachments (see zip file)	FVC Day 42 Change from Baseline.pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: SBP Change from baseline Day 42

End point title	SBP Change from baseline 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:	
Day 42	

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	98		
Units: mmHg				
arithmetic mean (standard deviation)	2 (± 10)	2.6 (± 9.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: DBP Change from baseline Day 42

End point title	DBP Change from baseline Day 42
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End point description:

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

End point type	Secondary
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End point timeframe:

Day 42

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	98		
Units: mmHg				
arithmetic mean (standard deviation)	-0.7 (± 7.1)	0.7 (± 6.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: HR Change from baseline Day 1 Post dose

End point title	HR Change from baseline Day 1 Post dose
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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 were excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm were also excluded.

End point type	Secondary
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End point timeframe:

Day 1

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[57]	96 ^[58]		
Units: bmp				
arithmetic mean (standard deviation)	-1.9 (± 6.8)	-2 (± 7.1)		

Notes:

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

[58] - 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 Day 1 post dose

End point title	QTcF Change from baseline Day 1 post dose
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 were excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm were also excluded.	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[59]	96 ^[60]		
Units: ms				
arithmetic mean (standard deviation)	-0.7 (± 11.2)	0.6 (± 10.2)		

Notes:

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

[60] - 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 Day 1 post dose

End point title	QRS Change from baseline Day 1 post dose
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 were excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm were also excluded.	
End point type	Secondary
End point timeframe:	
Day 1	

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[61]	96 ^[62]		
Units: ms				
arithmetic mean (standard deviation)	0.8 (± 3.8)	0.5 (± 3.8)		

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.

Statistical analyses

No statistical analyses for this end point

Secondary: QTcF Change from baseline Day 42 Post dose

End point title	QTcF Change from baseline Day 42 Post dose
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 were excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm were also excluded.	
End point type	Secondary
End point timeframe: Day 42	

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[63]	96 ^[64]		
Units: ms				
arithmetic mean (standard deviation)	1.8 (± 14.1)	-1 (± 14.1)		

Notes:

[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

No statistical analyses for this end point

Secondary: HR Change from baseline Day 42 Post dose

End point title	HR Change from baseline Day 42 Post dose
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 were excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm were also excluded.	
End point type	Secondary
End point timeframe: Day 42	

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[65]	96 ^[66]		
Units: bpm				
arithmetic mean (standard deviation)	-3.6 (± 8.9)	-2.2 (± 10.8)		

Notes:

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

[66] - 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 Day 42 post dose

End point title	PR Change from baseline Day 42 post dose
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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 were excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm were also excluded.

End point type	Secondary
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End point timeframe:

Day 42

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[67]	96 ^[68]		
Units: ms				
arithmetic mean (standard deviation)	0.9 (± 12.9)	1.1 (± 11.5)		

Notes:

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

[68] - 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 Day 1 post dose

End point title	PR Change from baseline Day 1 post dose
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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 were excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm were also excluded.

End point type	Secondary
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End point timeframe:

Day 1

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[69]	96 ^[70]		
Units: ms				
arithmetic mean (standard deviation)	-1 (± 8.5)	-0.8 (± 9.5)		

Notes:

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

[70] - 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 Day 42 post dose

End point title	QRS Change from baseline Day 42 post dose
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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 were excluded from this summary. ECGs at a timepoint with Atrial Fibrillation, Atrial Flutter or Ectopic Supraventricular Rhythm were also excluded.

End point type	Secondary
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End point timeframe:

Day 42

End point values	CHF5259 pMDI - safety population	Placebo pMDI - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95 ^[71]	96 ^[72]		
Units: ms				
arithmetic mean (standard deviation)	0.4 (± 4.7)	-0.1 (± 5.3)		

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.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage asthma control days

End point title	Percentage asthma control days
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End point description:

An asthma control day is derived from patient diary data, and is defined as any day during the treatment period that has a total asthma score of 0 (nighttime plus daytime) and where no rescue medication was used.

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

End point type	Secondary
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End point timeframe:

Daily during run-in and treatment periods.

End point values	CHF5259 pMDI - ITT population	Placebo pMDI - ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97 ^[73]	97 ^[74]		
Units: percent				
arithmetic mean (standard deviation)	21.7 (± 32.3)	19.4 (± 28.5)		

Notes:

[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	CHF 5259 pMDI vs Placebo pMDI
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Statistical analysis description:

In a Cross-over study, groups examined should not be added up. The number N=194 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	CHF5259 pMDI - ITT population v Placebo pMDI - ITT population
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority ^[75]
P-value	= 0.188
Method	ANOVA
Parameter estimate	Adjusted mean difference
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	6.2

Notes:

[75] - Percentage of Daily Asthma Control Days was analysed by means of an ANOVA model with treatment, patient and period as fixed effects

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At each visit, from screening (Visit 1) to follow-up (Visit 6) or, in case, at early termination

Adverse event reporting additional description:

Overall, 31 TEAEs were reported in 20 (20.4%) patients during the treatment periods. The number of TEAEs was higher during treatment with CHF 5259 pMDI than placebo, but the number of patients was similar between the treatments (20 events in 13 [13.4%] patients with CHF 5259 and 11 events in 11 [11.2%] patients with placebo).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	CHF5259 pMDI
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Reporting group description:

No serious TEAEs, ADRs, serious ADRs, TEAEs leading to study discontinuation or TEAEs leading to death were reported during the study.

Reporting group title	Placebo pMDI
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Reporting group description:

No serious TEAEs, ADRs, serious ADRs, TEAEs leading to study discontinuation or TEAEs leading to death were reported during the study.

Serious adverse events	CHF5259 pMDI	Placebo pMDI	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 97 (0.00%)	0 / 98 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	CHF5259 pMDI	Placebo pMDI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 97 (13.40%)	11 / 98 (11.22%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Chest pain subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Asthma	Additional description: 1 mild TEAE of worsening asthma symptoms was reported for one patient during treatment with placebo. This TEAE was not considered by the investigator as an episode of asthma exacerbation.		
subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 98 (1.02%) 1	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 98 (1.02%) 1	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Investigations Weight increased subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	0 / 98 (0.00%) 0	
Blood pressure increased subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Transaminases increased subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 98 (1.02%) 1	
Injury, poisoning and procedural complications Forearm fracture subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 98 (1.02%) 1	
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 98 (1.02%) 1	

Neuritis subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Eye disorders Eye irritation subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Gastrointestinal disorders Gastritis subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	1 / 98 (1.02%) 1	
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Musculoskeletal and connective tissue disorders Intervertebral disc disorder subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	4 / 97 (4.12%) 4	3 / 98 (3.06%) 3	
Fungal skin infection subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 98 (1.02%) 1	
Influenza subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 98 (0.00%) 0	
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 98 (1.02%) 1	
Periodontitis			

subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Skin bacterial infection			
subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	
occurrences (all)	1	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: