



Clinical trial results:

A first in human randomised, double-blind, placebo-controlled study of single ascending doses in healthy male volunteers and repeated ascending dose in asthmatic patients followed by a 3-way cross-over, placebo-controlled, single-dose in COPD patients to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of CHF6366

Summary

EudraCT number	2015-005551-27
Trial protocol	GB
Global end of trial date	18 April 2019

Results information

Result version number	v1 (current)
This version publication date	03 May 2020
First version publication date	03 May 2020

Trial information

Trial identification

Sponsor protocol code	CCD-06366AA1-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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., 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	10 February 2020
Is this the analysis of the primary completion data?	No
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Global end of trial reached?	Yes
Global end of trial date	18 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the safety and tolerability of single ascending doses of CHF 6366 in healthy male volunteers, of repeated ascending doses in male and female patients with asthma , and of a single dose in male patients with COPD.

CHF 6366 is a new chemical entity with muscarinic antagonist and β 2 receptor agonist (MABA) properties, which is being developed by Chiesi for treatment of asthma and COPD. The parent compound CHF 6366 is metabolised to the metabolites CHF 6387 and CHF 6361.

The study consisted of 3 independent parts:

Part 1: Randomised, placebo-controlled, double-blind, single dose-escalation, alternating cross-over design, in 3 cohorts of healthy male subjects.

Part 2: Randomised, placebo-controlled, double-blind, repeated dose-escalation, parallel group design, in 4 cohorts of subjects with asthma.

Part 3: Randomised, placebo-controlled (double-blind), active-controlled (open-label), single-dose, 3-way cross-over design, in subjects with COPD.

Protection of trial subjects:

The study was conducted according to the clinical study protocol, according with the principles of the Declaration of Helsinki, and local regulations, as well as according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP) (ICH/CPMP/135/95).

AEs and vital signs were recorded at all visits (from screening onward). Based on the medical opinion of the Investigator, all new clinically relevant abnormalities or significant changes at the study visits were reported as AEs in the electronic case report form (eCRF). All PK and safety assessments were performed according to accepted methods.

Part 1: The dose-escalation was alternated between the 3 cohorts (Cohorts A, B, and H). Eight of 12 subjects in each treatment period received CHF 6366 and 4 subjects received placebo. A sentinel/staggered dosing was followed to ensure additional safety of the subjects. A sentinel group of 2 subjects (1 active and 1 placebo) were initially dosed at least 24 hours in advance of the other subjects in each cohort. The other 10 subjects of the cohort were dosed only after a safety review of data from the sentinels by the Safety Advisory Committee (SAC). From Dose 2 to Dose 7 (i.e., 10 μ g to 360 μ g), the administered doses could be modified based on safety and PK data review. Stopping rules were in place.

Part 2: Started only after completion and review of the safety data from Part 1. A similar approach as for Part 1 was used (sentinel/staggered dosing), to ensure additional safety of the subjects. Rules for increasing the dose followed a defined criterion. Stopping rules were in place. SAC reviewed the safety and available PK data before next dose increase.

Part 3: Drug administration started after the completion and review of the safety data of the entire Part 1 of the study.

Background therapy:

There was no background therapy used in this trial.

Abbreviations used in this database entry:

AE=Adverse event

Anoro=ANORO ELLIPTA 55 micrograms/22 micrograms inhalation powder, pre-dispensed

AUC(0-12h)=The area under the plasma concentration curve observed from 0 to 12 hours post-dose was computed using the linear trapezoidal rule

bid=Twice daily

BLQ=Below the limit of quantification

BP=Blood pressure

bpm=Beats per minute

Cmax=Maximum plasma concentration

DB=Double-blind

DPI=Dry-powder inhaler

Cmax=Maximum plasma concentration

COPD=Chronic obstructive pulmonary disease

CSR=Clinical study report

DBP=Diastolic blood pressure

eCRF=Electronic case report form

ECG=Electrocardiogram

FEV1=Forced expiratory volume in 1 second

HR=Heart rate

IMP=Investigational medicinal product

MABA=Muscarinic antagonist and β 2 receptor agonist

MAPK=Mitogen-activated protein kinases

MD=Multiple Dose Level (as in MD1, MD2, MD3, MD4)

mg=Milligram

ms=Millisecond

μ g=Microgram

N=Number of subjects

ND=Not determined

PBO-controlled=Placebo-controlled

PI=Principal investigator

PK=Pharmacokinetic

QTcF=QT interval, corrected using Fridericia's formula

SAC=Safety Advisory Committee

SAE=Serious adverse event

SBP=Systolic blood pressure

SD1=Single Dose Level 1

SD2=Single Dose Level 2

TEAEs=Treatment-emergent adverse events

$t_{1/2}$ =Terminal (apparent elimination) half-life

Tmax=Time of the maximum plasma concentration

Evidence for comparator: -

Actual start date of recruitment	28 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 106
Worldwide total number of subjects	106
EEA total number of subjects	106

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)	95
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy adult male subjects (N=34), male and female patients diagnosed with asthma (N=48) or with COPD (N=24) were screened according to the study inclusion and exclusion criteria.

Signed Informed Consent Form was obtained prior to any study-related procedures.

Pre-assignment

Screening details:

Screening visit was 3 - 28 days (depending on the part of the study), before the first administration of the study treatment. For healthy subjects, none of the vital signs, ECG results, or lung function data, and physical examination were considered abnormal or clinically relevant. For asthma and COPD inclusion and exclusion criteria were observed.

Period 1

Period 1 title	Treatment Study Parts 1, 2, 3 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Blinding was as follows:

Part 1: Placebo-controlled, double-blind, healthy subjects

Part 2: Placebo-controlled, double-blind, subjects with asthma

Part 3: Placebo-controlled (double-blind), active-controlled (open-label), subjects with COPD

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 - Cohort A - Healthy subjects

Arm description:

Part 1: Single ascending dose in healthy subjects.

Randomised, placebo-controlled, double blind, single dose-escalation, alternating cross-over design in 3 cohorts (A, B, and H) of healthy male subjects.

During Part 1, seven single doses of CHF 6366 were administered according to an escalation scheme. The dose-escalation was alternated between the 3 cohorts (Cohorts A, B, and H).

Subjects in Cohort A received 3 ascending doses of CHF 6366: 5 µg (Dose 1), 20 µg (Dose 3), and 80 µg (Dose 5).

Cohort H: consisted of 3 subjects from Cohort A and 9 subjects from Cohort B. Subjects in Cohort H received 1 ascending dose: 360 µg (Dose 7).

Arm type	Experimental
Investigational medicinal product name	CHF 6366
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1: Single ascending dose – Healthy subjects

CHF 6366 was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser.

Seven single doses of CHF 6366 were administered according to an escalation scheme.

Study Part 1 was run according to an alternating crossover design with 3 cohorts of healthy male subjects (cohort A, cohort B, cohort H), with an alternating crossover design, for a given subject. Each subject participated in 3 or 4 treatment periods (alternating dose levels). The washout between 2 consecutive treatments was at least 14 days.

- Subjects in Cohort A received 3 ascending doses of CHF 6366: 5 µg (Dose 1), 20 µg (Dose 3), and 80 µg (Dose 5)
- Subjects in Cohort B received 3 ascending doses of CHF 6366: 10 µg (Dose 2), 40 µg (Dose 4), and 160 µg (Dose 6)
- Subjects in Cohort H received 1 ascending dose of CHF 6366: 360 µg (Dose 7)

Investigational medicinal product name	CHF 6366 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1, Part 2, Part 3 -- Placebo

CHF 6366 placebo was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser, according to the randomisation scheme.

Arm title	Part 1 - Cohort B - Healthy subjects
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Arm description:

Part 1: Single ascending dose in healthy subjects.

Randomised, placebo-controlled, double blind, single dose-escalation, alternating cross-over design in 3 cohorts (A, B, and H) of healthy male subjects.

During Part 1, seven single doses of CHF 6366 were administered according to an escalation scheme. The dose-escalation was alternated between the 3 cohorts (Cohorts A, B, and H).

Subjects in Cohort B received 3 ascending doses of CHF 6366: 10 µg (Dose 2), 40 µg (Dose 4), and 160 µg (Dose 6).

Cohort H: consisted of 3 subjects from Cohort A and 9 subjects from Cohort B. Subjects in Cohort H received 1 ascending dose: 360 µg (Dose 7).

Arm type	Experimental
Investigational medicinal product name	CHF 6366
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1: Single ascending dose – Healthy subjects

CHF 6366 was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser.

Seven single doses of CHF 6366 were administered according to an escalation scheme.

Study Part 1 was run according to an alternating crossover design with 3 cohorts of healthy male subjects (cohort A, cohort B, cohort H), with an alternating crossover design, for a given subject. Each subject participated in 3 or 4 treatment periods (alternating dose levels). The washout between 2 consecutive treatments was at least 14 days.

- Subjects in Cohort A received 3 ascending doses of CHF 6366: 5 µg (Dose 1), 20 µg (Dose 3), and 80 µg (Dose 5)
- Subjects in Cohort B received 3 ascending doses of CHF 6366: 10 µg (Dose 2), 40 µg (Dose 4), and 160 µg (Dose 6)
- Subjects in Cohort H received 1 ascending dose of CHF 6366: 360 µg (Dose 7)

Investigational medicinal product name	CHF 6366 - Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1, Part 2, Part 3 -- Placebo

CHF 6366 placebo was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser, according to the randomisation scheme.

Arm title	Part 2 - Cohort C - Asthma - CHF 6366 - 40 µg
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Arm description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort C received 40 µg of CHF 6366, once daily for 7 days.

Arm type	Experimental
Investigational medicinal product name	CHF 6366
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 2: Multiple ascending dose of CHF 6366 – Subjects with asthma

CHF 6366 was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser.

Four multiple doses of CHF 6366 were administered once daily for 7 days, according to an escalation scheme.

In study Part 2, subjects were divided into 4 dose cohorts (Cohorts C, D, E, and F) and randomised to receive either CHF 6366 or placebo once daily for 7 days.

- Subjects in Cohort C received: 40 µg (MD1) total daily dose
- Subjects in Cohort D received: 80 µg (MD2) total daily dose
- Subjects in Cohort E received: 160 µg (MD3) total daily dose
- Subjects in Cohort F received: 240 µg (MD4) total daily dose

Investigational medicinal product name	CHF 6366 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1, Part 2, Part 3 -- Placebo

CHF 6366 placebo was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser, according to the randomisation scheme.

Arm title	Part 2 - Cohort D - Asthma - CHF 6366 - 80 µg
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Arm description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort D received 80 µg of CHF 6366, once daily for 7 days.

Arm type	Experimental
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Investigational medicinal product name	CHF 6366
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 2: Multiple ascending dose of CHF 6366 – Subjects with asthma

CHF 6366 was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser.

Four multiple doses of CHF 6366 were administered once daily for 7 days, according to an escalation scheme.

In study Part 2, subjects were divided into 4 dose cohorts (Cohorts C, D, E, and F) and randomised to receive either CHF 6366 or placebo once daily for 7 days.

- Subjects in Cohort C received: 40 µg (MD1) total daily dose
- Subjects in Cohort D received: 80 µg (MD2) total daily dose
- Subjects in Cohort E received: 160 µg (MD3) total daily dose
- Subjects in Cohort F received: 240 µg (MD4) total daily dose

Investigational medicinal product name	CHF 6366 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1, Part 2, Part 3 -- Placebo

CHF 6366 placebo was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser, according to the randomisation scheme.

Arm title	Part 2 - Cohort E - Asthma - CHF 6366 - 160 µg
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Arm description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort E received 160 µg of CHF 6366, once daily for 7 days.

Arm type	Experimental
Investigational medicinal product name	CHF 6366
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 2: Multiple ascending dose of CHF 6366 – Subjects with asthma

CHF 6366 was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser.

Four multiple doses of CHF 6366 were administered once daily for 7 days, according to an escalation scheme.

In study Part 2, subjects were divided into 4 dose cohorts (Cohorts C, D, E, and F) and randomised to receive either CHF 6366 or placebo once daily for 7 days.

- Subjects in Cohort C received: 40 µg (MD1) total daily dose
- Subjects in Cohort D received: 80 µg (MD2) total daily dose
- Subjects in Cohort E received: 160 µg (MD3) total daily dose

- Subjects in Cohort F received: 240 µg (MD4) total daily dose

Investigational medicinal product name	CHF 6366 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1, Part 2, Part 3 -- Placebo

CHF 6366 placebo was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser, according to the randomisation scheme.

Arm title	Part 2 - Cohort F - Asthma - CHF 6366 - 240 µg
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Arm description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort F received 240 µg of CHF 6366, once daily for 7 days.

Arm type	Experimental
Investigational medicinal product name	CHF 6366
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 2: Multiple ascending dose of CHF 6366 – Subjects with asthma

CHF 6366 was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser.

Four multiple doses of CHF 6366 were administered once daily for 7 days, according to an escalation scheme.

In study Part 2, subjects were divided into 4 dose cohorts (Cohorts C, D, E, and F) and randomised to receive either CHF 6366 or placebo once daily for 7 days.

- Subjects in Cohort C received: 40 µg (MD1) total daily dose
- Subjects in Cohort D received: 80 µg (MD2) total daily dose
- Subjects in Cohort E received: 160 µg (MD3) total daily dose
- Subjects in Cohort F received: 240 µg (MD4) total daily dose

Investigational medicinal product name	CHF 6366 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1, Part 2, Part 3 -- Placebo

CHF 6366 placebo was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser, according to the randomisation scheme.

Arm title	Part 2 - Subjects with asthma - Placebo
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Arm description:

Part 2 of the study.

Subjects with asthma who received placebo for 7 days.

Arm type	Placebo
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Investigational medicinal product name	CHF 6366 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1, Part 2, Part 3 -- Placebo

CHF 6366 placebo was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser, according to the randomisation scheme.

Arm title	Part 3 - Subjects with COPD
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Arm description:

Part 3 – Single dose in subjects with COPD.

Randomised, placebo-controlled (double-blind), active-controlled (open-label), single-dose, 3-way crossover design.

After completion and review of the safety data of the entire Part 1 of the study, one dose of the study drug was administered to a cohort of subjects with COPD, according to a randomised, placebo controlled, active-controlled*, single-dose, 3-way cross-over design. The washout time between the 3 treatments was at least 7 days.

*The active control was Anoro [Anoro Ellipta (umeclidinium and vilanterol dry powder inhaler, 55/22 µg)].

Arm type	Experimental
Investigational medicinal product name	CHF 6366
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 3: Single dose of CHF 6366 – Subjects with COPD

CHF 6366 was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser.

In study Part 3, subjects with COPD received a single dose of either 240 µg CHF 6366, Anoro (active comparator), or placebo, according to a randomisation scheme.

Investigational medicinal product name	CHF 6366 - Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Part 1, Part 2, Part 3 -- Placebo

CHF 6366 placebo was a colourless, aqueous, isotonic solution, administered as oral inhalation in the morning through e-Flow Rapid (PARI) nebuliser, according to the randomisation scheme.

Investigational medicinal product name	Anoro Ellipta
Investigational medicinal product code	ATC code: R03AL03
Other name	Umeclidinium and Vilanterol dry powder inhaler, 55/22 µg
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Part 3: Single dose of Anoro Ellipta – Subjects with COPD

In part 3, a single dose of anoro ellipta (umeclidinium and vilanterol dry powder inhaler, 55/22 µg) was administered as oral inhalation in the morning through Ellipta inhaler, according to the randomisation

scheme.

Number of subjects in period 1	Part 1 - Cohort A - Healthy subjects	Part 1 - Cohort B - Healthy subjects	Part 2 - Cohort C - Asthma - CHF 6366 - 40 µg
Started	18	16	9
Completed	12	12	8
Not completed	6	4	1
Consent withdrawn by subject	6	-	1
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	-	1	-
CHF provide brief reason for disont	-	3	-

Number of subjects in period 1	Part 2 - Cohort D - Asthma - CHF 6366 - 80 µg	Part 2 - Cohort E - Asthma - CHF 6366 - 160 µg	Part 2 - Cohort F - Asthma - CHF 6366 - 240 µg
Started	9	9	9
Completed	8	9	9
Not completed	1	0	0
Consent withdrawn by subject	1	-	-
Physician decision	-	-	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	-	-	-
CHF provide brief reason for disont	-	-	-

Number of subjects in period 1	Part 2 - Subjects with asthma - Placebo	Part 3 - Subjects with COPD
Started	12	24
Completed	12	21
Not completed	0	3
Consent withdrawn by subject	-	-
Physician decision	-	1
Adverse event, non-fatal	-	2
Lost to follow-up	-	-
CHF provide brief reason for disont	-	-

Baseline characteristics

Reporting groups

Reporting group title	Part 1 - Cohort A - Healthy subjects
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Reporting group description:

Part 1: Single ascending dose in healthy subjects.

Randomised, placebo-controlled, double blind, single dose-escalation, alternating cross-over design in 3 cohorts (A, B, and H) of healthy male subjects.

During Part 1, seven single doses of CHF 6366 were administered according to an escalation scheme. The dose-escalation was alternated between the 3 cohorts (Cohorts A, B, and H).

Subjects in Cohort A received 3 ascending doses of CHF 6366: 5 µg (Dose 1), 20 µg (Dose 3), and 80 µg (Dose 5).

Cohort H: consisted of 3 subjects from Cohort A and 9 subjects from Cohort B. Subjects in Cohort H received 1 ascending dose: 360 µg (Dose 7).

Reporting group title	Part 1 - Cohort B - Healthy subjects
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Reporting group description:

Part 1: Single ascending dose in healthy subjects.

Randomised, placebo-controlled, double blind, single dose-escalation, alternating cross-over design in 3 cohorts (A, B, and H) of healthy male subjects.

During Part 1, seven single doses of CHF 6366 were administered according to an escalation scheme. The dose-escalation was alternated between the 3 cohorts (Cohorts A, B, and H).

Subjects in Cohort B received 3 ascending doses of CHF 6366: 10 µg (Dose 2), 40 µg (Dose 4), and 160 µg (Dose 6).

Cohort H: consisted of 3 subjects from Cohort A and 9 subjects from Cohort B. Subjects in Cohort H received 1 ascending dose: 360 µg (Dose 7).

Reporting group title	Part 2 - Cohort C - Asthma - CHF 6366 - 40 µg
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Reporting group description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort C received 40 µg of CHF 6366, once daily for 7 days.

Reporting group title	Part 2 - Cohort D - Asthma - CHF 6366 - 80 µg
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Reporting group description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort D received 80 µg of CHF 6366, once daily for 7 days.

Reporting group title	Part 2 - Cohort E - Asthma - CHF 6366 - 160 µg
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Reporting group description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort E received 160 µg of CHF 6366, once daily for 7 days.

Reporting group title	Part 2 - Cohort F - Asthma - CHF 6366 - 240 µg
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Reporting group description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort F received 240 µg of CHF 6366, once daily for 7 days.

Reporting group title	Part 2 - Subjects with asthma - Placebo
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Reporting group description:

Part 2 of the study.

Subjects with asthma who received placebo for 7 days.

Reporting group title	Part 3 - Subjects with COPD
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Reporting group description:

Part 3 – Single dose in subjects with COPD.

Randomised, placebo-controlled (double-blind), active-controlled (open-label), single-dose, 3-way crossover design.

After completion and review of the safety data of the entire Part 1 of the study, one dose of the study drug was administered to a cohort of subjects with COPD, according to a randomised, placebo controlled, active-controlled*, single-dose, 3-way cross-over design. The washout time between the 3 treatments was at least 7 days.

*The active control was Anoro [Anoro Ellipta (umeclidinium and vilanterol dry powder inhaler, 55/22 µg)].

Reporting group values	Part 1 - Cohort A - Healthy subjects	Part 1 - Cohort B - Healthy subjects	Part 2 - Cohort C - Asthma - CHF 6366 - 40 µg
Number of subjects	18	16	9
Age categorical Units: Subjects			
Adults (18-64 years)	18	16	9
From 65-84 years	0	0	0
Age continuous Units: years			
arithmetic mean	36.9	32.9	39.9
standard deviation	± 9.6	± 9.2	± 17.9
Gender categorical Units: Subjects			
Female	0	0	3
Male	18	16	6
Body mass index Units: kg/m ²			
arithmetic mean	26.50	25.92	25.69
standard deviation	± 3.2	± 3.02	± 3.31

Reporting group values	Part 2 - Cohort D - Asthma - CHF 6366 - 80 µg	Part 2 - Cohort E - Asthma - CHF 6366 - 160 µg	Part 2 - Cohort F - Asthma - CHF 6366 - 240 µg
Number of subjects	9	9	9
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	9
From 65-84 years	0	0	0

Age continuous Units: years arithmetic mean standard deviation	38.3 ± 11.4	34.6 ± 10.0	36.2 ± 9.2
Gender categorical Units: Subjects			
Female	4	3	4
Male	5	6	5
Body mass index Units: kg/m2 arithmetic mean standard deviation	29.08 ± 4.89	26.74 ± 5.20	29.62 ± 7.06

Reporting group values	Part 2 - Subjects with asthma - Placebo	Part 3 - Subjects with COPD	Total
Number of subjects	12	24	106
Age categorical Units: Subjects			
Adults (18-64 years)	12	13	95
From 65-84 years	0	11	11
Age continuous Units: years arithmetic mean standard deviation	41.4 ± 9.4	61.9 ± 8.0	-
Gender categorical Units: Subjects			
Female	3	10	27
Male	9	14	79
Body mass index Units: kg/m2 arithmetic mean standard deviation	25.39 ± 2.23	27.40 ± 3.91	-

End points

End points reporting groups

Reporting group title	Part 1 - Cohort A - Healthy subjects
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Reporting group description:

Part 1: Single ascending dose in healthy subjects.

Randomised, placebo-controlled, double blind, single dose-escalation, alternating cross-over design in 3 cohorts (A, B, and H) of healthy male subjects.

During Part 1, seven single doses of CHF 6366 were administered according to an escalation scheme. The dose-escalation was alternated between the 3 cohorts (Cohorts A, B, and H).

Subjects in Cohort A received 3 ascending doses of CHF 6366: 5 µg (Dose 1), 20 µg (Dose 3), and 80 µg (Dose 5).

Cohort H: consisted of 3 subjects from Cohort A and 9 subjects from Cohort B. Subjects in Cohort H received 1 ascending dose: 360 µg (Dose 7).

Reporting group title	Part 1 - Cohort B - Healthy subjects
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Reporting group description:

Part 1: Single ascending dose in healthy subjects.

Randomised, placebo-controlled, double blind, single dose-escalation, alternating cross-over design in 3 cohorts (A, B, and H) of healthy male subjects.

During Part 1, seven single doses of CHF 6366 were administered according to an escalation scheme. The dose-escalation was alternated between the 3 cohorts (Cohorts A, B, and H).

Subjects in Cohort B received 3 ascending doses of CHF 6366: 10 µg (Dose 2), 40 µg (Dose 4), and 160 µg (Dose 6).

Cohort H: consisted of 3 subjects from Cohort A and 9 subjects from Cohort B. Subjects in Cohort H received 1 ascending dose: 360 µg (Dose 7).

Reporting group title	Part 2 - Cohort C - Asthma - CHF 6366 - 40 µg
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Reporting group description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort C received 40 µg of CHF 6366, once daily for 7 days.

Reporting group title	Part 2 - Cohort D - Asthma - CHF 6366 - 80 µg
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Reporting group description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort D received 80 µg of CHF 6366, once daily for 7 days.

Reporting group title	Part 2 - Cohort E - Asthma - CHF 6366 - 160 µg
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Reporting group description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort E received 160 µg of CHF 6366, once daily for 7 days.

Reporting group title	Part 2 - Cohort F - Asthma - CHF 6366 - 240 µg
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Reporting group description:

Part 2 – Multiple ascending dose in subjects with asthma.

Randomised, placebo-controlled, double blind, repeated dose-escalation, parallel group design in 4 dose cohorts (Cohorts C, D, E, and F). Subjects were randomised to receive either CHF 6366 or placebo, once daily for 7 days.

Subjects in cohort F received 240 µg of CHF 6366, once daily for 7 days.

Reporting group title	Part 2 - Subjects with asthma - Placebo
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Reporting group description:

Part 2 of the study.

Subjects with asthma who received placebo for 7 days.

Reporting group title	Part 3 - Subjects with COPD
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Reporting group description:

Part 3 – Single dose in subjects with COPD.

Randomised, placebo-controlled (double-blind), active-controlled (open-label), single-dose, 3-way crossover design.

After completion and review of the safety data of the entire Part 1 of the study, one dose of the study drug was administered to a cohort of subjects with COPD, according to a randomised, placebo controlled, active-controlled*, single-dose, 3-way cross-over design. The washout time between the 3 treatments was at least 7 days.

*The active control was Anoro [Anoro Ellipta (umeclidinium and vilanterol dry powder inhaler, 55/22 µg)].

Subject analysis set title	Part 1 - Cohort A - Healthy subjects
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects in Cohort A received 3 ascending doses of CHF 6366: 5 µg (Dose 1), 20 µg (Dose 3), and 80 µg (Dose 5), or placebo.

Subject analysis set title	Part 1 - Cohort B - Healthy subjects
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects in Cohort B received 3 ascending doses CHF 6366: 10 µg (Dose 2), 40 µg (Dose 4), and 160 µg (Dose 6), or placebo.

Subject analysis set title	Part 1 - Cohort H - Healthy subjects
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Subjects in Cohort H received 1 ascending dose: 360 µg (Dose 7) or placebo.

Subject analysis set title	Part 1 - Healthy subjects - CHF 6366, 5 µg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 5 µg.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 1 - Healthy subjects - CHF 6366, 10 µg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 10 µg.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 1 - Healthy subjects - CHF 6366, 20 µg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 20 µg.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 1 - Healthy subjects - CHF 6366, 40 µg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 40 µg.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 1 - Healthy subjects - CHF 6366, 80 µg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 80 µg.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 1 - Healthy subjects - CHF 6366, 160 µg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 160 µg.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 1 - Healthy subjects - CHF 6366, 360 µg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 360 µg.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 1 - Healthy subjects - Placebo
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 1 of the study.

Healthy subjects who received placebo.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 2 - Subjects with asthma - CHF 6366, 40 µg
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Part 2 of the study.

Subjects with asthma who received multiple ascending dose of CHF 6366, 40 µg for 7 days, according to the escalation scheme.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 2 - Subjects with asthma - CHF 6366, 80 µg
Subject analysis set type	Safety analysis

Subject analysis set description:

Part 2 of the study.

Subjects with asthma who received multiple ascending dose of CHF 6366, 80 µg for 7 days, according to the escalation scheme.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 2 - Subjects with asthma - CHF 6366, 160 µg
Subject analysis set type	Safety analysis

Subject analysis set description:

Part 2 of the study.

Subjects with asthma who received multiple ascending dose of CHF 6366, 160 µg for 7 days, according to the escalation scheme.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject analysis set type	Safety analysis

Subject analysis set description:

Part 2 of the study.

Subjects with asthma who received multiple ascending dose of CHF 6366, 240 µg for 7 days, according to the escalation scheme.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 2 - Subjects with asthma - Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Part 2 of the study.

Subjects with asthma who received placebo for 7 days.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 3 - Subjects with COPD - CHF 6366, 240 µg
Subject analysis set type	Safety analysis

Subject analysis set description:

Part 3 of the study.

Subjects with COPD who received a single dose of CHF 6366, 240 µg, according to the randomisation scheme.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 3 - Subjects with COPD - Anoro, 55/22 µg
Subject analysis set type	Safety analysis

Subject analysis set description:

Part 3 of the study.

Subjects with COPD who received a single dose of Anoro, 55/22 µg, according to the randomisation scheme.

For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.

Subject analysis set title	Part 3 - Subjects with COPD - Placebo
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Subject analysis set type	Safety analysis
Subject analysis set description: Part 3 of the study.	
Subjects with COPD who received a single dose of Placebo, according to the randomisation scheme.	
For pragmatic reasons to complete this database entry, this subject analysis set was also used to represent the Pharmacodynamic population and Pharmacokinetic population.	

Primary: 1_Part 1 - SBP and DBP - Single ascending dose - Healthy subjects - Any post-dose timepoint

End point title	1_Part 1 - SBP and DBP - Single ascending dose - Healthy subjects - Any post-dose timepoint ^[1]
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End point description:

2_Part 1 - SBP and DBP - Healthy subjects Cohorts A, B, H - Any post-dose timepoint.

Data were derived from manual measurements by the study staff.

Baseline is defined as pre-dose value on Day 1 of each treatment for Cohorts A and B and last non-missing schedule value prior to dosing with study medication for Cohort H.

Presented are representative results of the time points.

The number of subjects from contributing to the data is indicated (Cohort A, B, and H).

In Cohort H, 3 subjects were from Cohort A and 9 subjects were from Cohort B; thus, in the Placebo column, the same subject was counted twice.

End point type	Primary
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End point timeframe:

On Day 1, at pre-dose and 15 min, 30 min, 1, 2, 4, 8, and 12 h post-dose.

On Day 2, at 24 h post-dose.

On Day 3, at 48 h post-dose, and at Follow-up.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 1 - Healthy subjects - CHF 6366, 5 µg	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg	Part 1 - Healthy subjects - CHF 6366, 40 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[2]	8	8	8
Units: subjects				
SBP change >20 mmHg	1	0	0	0
SBP change <-20 mmHg	0	0	0	0
DBP change >10 mmHg	2	0	1	0
DBP change <-10 mmHg	3	4	2	1

Notes:

[2] - Safety population was used for the analysis of each group.

End point values	Part 1 - Healthy subjects - CHF 6366, 80 µg	Part 1 - Healthy subjects - CHF 6366, 160 µg	Part 1 - Healthy subjects - CHF 6366, 360 µg	Part 1 - Healthy subjects - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	8	8	24 ^[3]
Units: subjects				

SBP change >20 mmHg	0	1	1	2
SBP change <-20 mmHg	0	0	0	2
DBP change >10 mmHg	1	2	0	4
DBP change <-10 mmHg	1	4	1	4

Notes:

[3] - N=28 see explanation in the endpoint description

Statistical analyses

No statistical analyses for this end point

Primary: 2_Part 1 - Heart rate (0-24h) - Single ascending dose - Healthy subjects - Change from baseline

End point title	2_Part 1 - Heart rate (0-24h) - Single ascending dose - Healthy subjects - Change from baseline ^[4]
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End point description:

Part 1 - Heart rate (0-24h) - Healthy subjects - Change from baseline.

Data were derived from measurements using 12-lead ECG, extracted from 24 h Holter monitoring.

Baseline is defined as the average HR of the 24 hours preceding the study drug administration on Day 1 of each treatment period.

Results show the value obtained for the adjusted difference vs placebo.

Adjusted mean difference and 90% CI based on a linear model with terms for treatment, period and sequence and subject within sequence as random effects and Baseline value as a covariate.

Presented are values extracted from Holter at pre-defined timepoints.

The number of subjects contributing to the data is indicated (Cohort A, B, and H).

End point type	Primary
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End point timeframe:

24h Holter ECG recording.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 1 - Healthy subjects - CHF 6366, 5 µg	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg	Part 1 - Healthy subjects - CHF 6366, 40 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[5]	8	8	8
Units: bpm				
number (confidence interval 90%)	-0.8 (-4.0 to 2.4)	-0.4 (-3.4 to 2.5)	-2.7 (-5.4 to 0.1)	0.4 (-2.3 to 3.0)

Notes:

[5] - Safety population was used for the analysis of each group.

Adjusted mean difference vs placebo.

End point values	Part 1 - Healthy subjects - CHF 6366, 80 µg	Part 1 - Healthy subjects - CHF 6366, 160 µg	Part 1 - Healthy subjects - CHF 6366, 360 µg	
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Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	8	8	
Units: bpm				
number (confidence interval 90%)	1.3 (-1.4 to 4.1)	2.4 (-0.6 to 5.4)	-0.1 (-6.0 to 5.7)	

Statistical analyses

No statistical analyses for this end point

Primary: 3_Part 1 - QTcF - Single ascending dose - Healthy subjects - Any post-dose timepoint

End point title	3_Part 1 - QTcF - Single ascending dose - Healthy subjects - Any post-dose timepoint ^[6]
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End point description:

Part 1 - QTcF - Single ascending dose - Healthy subjects - Any post-dose timepoint.

Data were derived from measurements using 12-lead ECG, extracted from 24 h Holter monitoring.

Baseline is defined as the time-matched measurement taken prior to the study drug administration on Day 1 (of each period for Cohorts A, B, and H).

Presented are values extracted from Holter at pre-defined timepoints.
The number of subjects contributing to the data is indicated.

In Cohort H, 3 subjects were from Cohort A and 9 from Cohort B, and thus in the Placebo column the same subject was counted twice.

End point type	Primary
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End point timeframe:

On Day 1 at pre-dose and 5, 15, 30, 45 min and 1, 1.5, 2, 4, 8, and 12 h post-dose.

On Day 2 at 24 h post-dose.

On Day 3 at 48 h post-dose and at Follow-up (if required).

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety. Evaluation of the safety data was done descriptively.

End point values	Part 1 - Healthy subjects - CHF 6366, 5 µg	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg	Part 1 - Healthy subjects - CHF 6366, 40 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[7]	8	8	8
Units: subjects				
450 < QTcF ≤ 480 msec	0	0	0	0
480 < QTcF ≤ 500 msec	0	0	0	0
QTcF > 500 msec	0	0	0	0
30 ≤ QTcF Increase from Baseline ≤ 60 msec	0	0	0	0
QTcF Increase from Baseline > 60 msec	0	0	0	0

Notes:

[7] - Safety population was used for the analysis of each group.

End point values	Part 1 - Healthy subjects - CHF 6366, 80 µg	Part 1 - Healthy subjects - CHF 6366, 160 µg	Part 1 - Healthy subjects - CHF 6366, 360 µg	Part 1 - Healthy subjects - Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	8	8	24 ^[8]
Units: subjects				
450 < QTcF ≤ 480 msec	0	0	0	0
480 < QTcF ≤ 500 msec	0	0	0	0
QTcF > 500 msec	0	0	0	0
30 ≤ QTcF Increase from Baseline ≤ 60 msec	0	0	0	0
QTcF Increase from Baseline > 60 msec	0	0	0	0

Notes:

[8] - N=28 (see explanation in the end point description)

Statistical analyses

No statistical analyses for this end point

Primary: 4_Part 1 - FEV1 - Single ascending dose - Healthy subjects - Decrease from baseline

End point title	4_Part 1 - FEV1 - Single ascending dose - Healthy subjects - Decrease from baseline ^[9]
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End point description:

Part 1 - FEV1 - Single ascending dose - Healthy subjects - Decrease from baseline FEV1 ≥ 20%

Data were derived from lung function measurements.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (Cohort A, B, and H).

End point type	Primary
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End point timeframe:

On Day 1, at pre-dose, 15, 30, 45 min and 1, 2, 6, and 12 h post-dose.

On Day 2, at 24 h post-dose.

On Day 3, at 48 h post-dose.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 1 - Healthy subjects - CHF 6366, 5 µg	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg	Part 1 - Healthy subjects - CHF 6366, 40 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed				
Units: subjects				
Decrease from baseline FEV1 ≥ 20%	0	0	0	0

End point values	Part 1 - Healthy subjects - CHF	Part 1 - Healthy subjects - CHF	Part 1 - Healthy subjects - CHF	Part 1 - Healthy subjects -
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	6366, 80 µg	6366, 160 µg	6366, 360 µg	Placebo
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed				
Units: subjects				
Decrease from baseline FEV1 ≥ 20%	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: 5_Part 2 - SBP and DBP - Multiple ascending dose - Subjects with Asthma - Any post-dose timepoint

End point title	5_Part 2 - SBP and DBP - Multiple ascending dose - Subjects with Asthma - Any post-dose timepoint ^[10]
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End point description:

SBP and DBP - Multiple ascending dose - Subjects with Asthma Cohorts C, D, E, F - Any post-dose timepoint.

Data were derived from manual measurements by the study staff.
Baseline is defined as pre-dose value on Day 1.

Presented are representative results of the time points.
The number of subjects contributing to the data is indicated (Cohort C, D, E, F).

End point type	Primary
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End point timeframe:

On Day 1 and on Day 7, at pre-dose and 15 and 30 min, 1, 2, 4, 8, and 12 h post-dose.
From Day 2, to Day 6 at pre-dose only.
On Day 8, at 24 h post-dose and at Follow-up.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.
The focus of the primary end points was safety.
Evaluation of the safety data was done descriptively.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9 ^[11]	9	9	9
Units: subjects				
SBP change >20 mmHg	0	1	0	0
SBP change <-20 mmHg	1	1	1	1
DBP change >10 mmHg	1	1	0	1
DBP change <-10 mmHg	2	3	4	7

Notes:

[11] - Safety population was used for the analysis of each group.

End point values	Part 2 - Subjects with asthma - Placebo			
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Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: subjects				
SBP change >20 mmHg	1			
SBP change <-20 mmHg	0			
DBP change >10 mmHg	1			
DBP change <-10 mmHg	3			

Statistical analyses

No statistical analyses for this end point

Primary: 6_Part 2 - Heart rate (0-24h) - Multiple ascending dose - Subjects with asthma - Change from baseline

End point title	6_Part 2 - Heart rate (0-24h) - Multiple ascending dose - Subjects with asthma - Change from baseline ^[12]
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End point description:

Part 2 - Heart rate (0-24h) - Multiple ascending dose -Subjects with asthma - Change from baseline

Data were derived from measurements using 12-lead ECG, extracted from 24 h Holter monitoring.

Baseline is defined as the average heart rate (in bpm) of the 24 hours preceding the study drug administration on Day 1.

Results show the value obtained for the adjusted difference vs placebo on Day 1 and Day 7. Adjusted mean difference and 90% CI based on a linear model with terms for treatment, period and sequence and subject within sequence as random effects and baseline value as a covariate.

Presented are values extracted from Holter at pre-defined timepoints.

The number of subjects contributing to the data is indicated (Cohort C, D, E, F).

End point type	Primary
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End point timeframe:

24h Holter ECG recording.

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9 ^[13]	9	9	9
Units: bpm				
number (confidence interval 90%)				
Day 1	4.5 (0.9 to 8.0)	0.3 (-3.5 to 4.1)	1.3 (-2.3 to 4.9)	1.9 (-1.7 to 5.6)
Day 7	4.3 (0.8 to 7.7)	0.6 (-3.1 to 4.2)	4.3 (0.9 to 7.7)	3.2 (-0.2 to 6.6)

Notes:

[13] - Safety population was used for the analysis of each group.

Statistical analyses

No statistical analyses for this end point

Primary: 7_Part 2 - QTcF - Multiple ascending dose - Subjects with asthma - Any post-dose timepoint

End point title	7_Part 2 - QTcF - Multiple ascending dose - Subjects with asthma - Any post-dose timepoint ^[14]
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End point description:

Part 2 - QTcF - Multiple ascending dose - Subjects with asthma - Any post-dose timepoint

Data were derived from measurements using 12-lead ECG, extracted from 24 h Holter monitoring.

Baseline for a particular post-baseline time point on Day X is defined as the time-matched measurement taken X days prior to the treatment administration.

Presented are values extracted from Holter at pre-defined timepoints.

The number of subjects contributing to the data is indicated (Cohort C, D, E, F).

End point type	Primary
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End point timeframe:

On Day 1, at pre-dose, 5, 15, 30, 45 min and 1, 1.5, 2, 4, 8, 12 h post-dose.

On Day 2, at 24 h after Day 1 dose.

On Day 7, at pre-dose, 15, 30 and 45 min and 1, 1.5, 2, 4, 8, 12 h post-dose.

On Day 8, 24-hours post-dose and at Follow-up.

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[15]	9	9	9
Units: subjects				
450 < QTcF ≤ 480 msec	0	0	0	0
480 < QTcF ≤ 500 msec	0	0	0	0
QTcF > 500 msec	0	0	0	0
30 ≤ QTcF Increase from Baseline ≤ 60 msec	1	0	0	2
QTcF Increase from Baseline > 60 msec	0	0	0	0

Notes:

[15] - Safety population was used for the analysis of each group.

End point values	Part 2 - Subjects with asthma - Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: subjects				
450 < QTcF ≤ 480 msec	0			
480 < QTcF ≤ 500 msec	0			
QTcF > 500 msec	0			

30 ≤ QTcF Increase from Baseline ≤ 60 msec	1			
QTcF Increase from Baseline > 60 msec	0			

Statistical analyses

No statistical analyses for this end point

Primary: 8_Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Change from baseline - Day 1

End point title	8_Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Change from baseline - Day 1 ^[16]
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End point description:

Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - FEV1 Change from baseline - Day 1

Data were derived from lung function measurements.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (Cohort C, D, E, and F).

End point type	Primary
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End point timeframe:

On Day 1 and Day 7, at pre-dose, 15, 30, and 45 min and 1, 2, 6, 12, and 24 h post-dose (Day 2).

On Day 8, at 24 h post-Day 7 dose.

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9 ^[17]	9 ^[18]	9	9
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
Day 1, 15 min	0.180 (0.070 to 0.290)	0.219 (0.014 to 0.424)	0.426 (0.120 to 0.731)	0.304 (0.022 to 0.587)
Day 1, 30 min	0.179 (0.023 to 0.335)	0.381 (0.168 to 0.595)	0.552 (0.248 to 0.856)	0.284 (0.019 to 0.550)
Day 1, 45 min	0.369 (0.219 to 0.519)	0.259 (0.058 to 0.460)	0.617 (0.309 to 0.925)	0.397 (0.176 to 0.618)
Day 1, 1 h	0.239 (0.067 to 0.411)	0.262 (0.037 to 0.488)	0.666 (0.357 to 0.974)	0.448 (0.204 to 0.691)
Day 1, 2 h	0.309 (0.154 to 0.464)	0.406 (0.193 to 0.618)	0.608 (0.360 to 0.855)	0.400 (0.129 to 0.671)
Day 1, 6 h	0.102 (-0.051 to 0.256)	0.243 (0.010 to 0.476)	0.558 (0.259 to 0.856)	0.350 (0.102 to 0.598)

Notes:

[17] - Safety population was used for the analysis of each group.

[18] -
N=9

N=8
N=9
N=9
N=9
N=9

End point values	Part 2 - Subjects with asthma - Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
Day 1, 15 min	-0.020 (-0.141 to 0.101)			
Day 1, 30 min	0.004 (-0.146 to 0.154)			
Day 1, 45 min	0.034 (-0.056 to 0.124)			
Day 1, 1 h	0.043 (-0.044 to 0.129)			
Day 1, 2 h	0.118 (0.003 to 0.234)			
Day 1, 6 h	0.045 (-0.074 to 0.164)			

Statistical analyses

No statistical analyses for this end point

Primary: 9_Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Change from pre-dose - Day 7

End point title	9_Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Change from pre-dose - Day 7 ^[19]
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End point description:

Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Change from pre-dose - Day 7.

Data were derived from lung function measurements.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (Cohort C, D, E, and F).

End point type	Primary
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End point timeframe:

On Day 1 and Day 7, at pre-dose, 15, 30, and 45 min and 1, 2, 6, 12, and 24 h post-dose (Day 2).

On Day 8, at 24 h post-Day 7 dose.

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[20]	8	9 ^[21]	9 ^[22]
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
Day 7, 15 min	0.441 (0.132 to 0.715)	0.371 (0.094 to 0.649)	0.412 (0.046 to 0.779)	0.260 (0.081 to 0.439)
Day 7, 30 min	0.410 (0.097 to 0.723)	0.540 (0.221 to 0.859)	0.443 (0.035 to 0.852)	0.376 (0.170 to 0.581)
Day 7, 45 min	0.480 (0.132 to 0.828)	0.575 (0.257 to 0.893)	0.468 (0.057 to 0.878)	0.464 (0.235 to 0.693)
Day 7, 1 h	0.466 (0.163 to 0.770)	0.688 (0.328 to 1.047)	0.488 (0.060 to 0.916)	0.379 (0.181 to 0.577)
Day 7, 2 h	0.561 (0.173 to 0.949)	0.685 (0.311 to 1.059)	0.450 (0.144 to 0.756)	0.415 (0.306 to 0.524)
Day 7, 6 h	0.384 (0.074 to 0.694)	0.439 (0.087 to 0.790)	0.288 (-0.057 to 0.632)	0.186 (0.066 to 0.305)

Notes:

[20] - Safety population was used for the analysis of each group.

[21] -

N=9

N=9

N=9

N=9

N=9

N=8

[22] -

N=9

N=9

N=8

N=9

N=8

N=9

End point values	Part 2 - Subjects with asthma - Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
Day 7, 15 min	0.106 (-0.055 to 0.267)			
Day 7, 30 min	0.064 (-0.043 to 0.171)			
Day 7, 45 min	0.125 (0.008 to 0.242)			
Day 7, 1 h	0.163 (0.031 to 0.294)			
Day 7, 2 h	0.208 (0.070 to 0.345)			
Day 7, 6 h	0.132 (-0.000 to 0.264)			

Statistical analyses

No statistical analyses for this end point

Primary: 10_Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Decrease from pre-dose \geq 20% - Day 7

End point title	10_Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Decrease from pre-dose \geq 20% - Day 7 ^[23]
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End point description:

Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Decrease from pre-dose \geq 20% - Day 7.

Data were derived from lung function measurements.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (Cohort C, D, E, and F).

End point type	Primary
----------------	---------

End point timeframe:

On Day 1 and Day 7, at pre-dose, 15, 30, and 45 min and 1, 2, 6, 12, and 24 h post-dose (Day 2).
On Day 8, at 24 h post-Day 7 dose.

Notes:

[23] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9 ^[24]	9	9	9
Units: subjects	0	0	0	0

Notes:

[24] - Safety population was used for the analysis of each group.

End point values	Part 2 - Subjects with asthma - Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: subjects	0			

Statistical analyses

Primary: 11_Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Decrease from baseline \geq 20% - Any post-dose timepoint

End point title	11_Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Decrease from baseline \geq 20% - Any post-dose timepoint ^[25]
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End point description:

Part 2 - FEV1 - Multiple ascending dose - Subjects with asthma - Decrease from baseline \geq 20% - Any post-dose timepoint

Data were derived from lung function measurements.

Baseline is defined as pre-dose value on Day 1.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (Cohort C, D, E, and F).

End point type	Primary
----------------	---------

End point timeframe:

On Day 1 and Day 7, at pre-dose, 15, 30, and 45 min and 1, 2, 6, 12, and 24 h post-dose (Day 2).

On Day 8, at 24 h post-Day 7 dose.

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 μ g	Part 2 - Subjects with asthma - CHF 6366, 80 μ g	Part 2 - Subjects with asthma - CHF 6366, 160 μ g	Part 2 - Subjects with asthma - CHF 6366, 240 μ g
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9 ^[26]	9	9	9
Units: subjects				
Day 1, 15 min	0	0	0	0
Day 1, 30 min	0	0	0	0
Day 1, 45 min	0	0	0	0
Day 1, 1 h	0	0	0	0
Day 1, 2 h	0	0	0	0
Day 1, 6 h	0	0	0	0

Notes:

[26] - Safety population was used for the analysis of each group.

End point values	Part 2 - Subjects with asthma - Placebo			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: subjects				
Day 1, 15 min	0			
Day 1, 30 min	0			
Day 1, 45 min	0			
Day 1, 1 h	0			
Day 1, 2 h	0			
Day 1, 6 h	0			

Statistical analyses

No statistical analyses for this end point

Primary: 12_Part 3 - SBP and DBP - Single dose - Subjects with COPD - Any post-dose timepoint

End point title	12_Part 3 - SBP and DBP - Single dose - Subjects with COPD - Any post-dose timepoint ^[27]
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End point description:

Part 3 - SBP and DBP - Multiple ascending dose - Subjects with COPD - Any post-dose timepoint.

Data were derived from manual measurements by the study staff.

Baseline is defined as pre-dose value on Day 1 of each treatment.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (subjects receiving CHF 6366, Anoro, Placebo).

End point type	Primary
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End point timeframe:

On Day 1, at pre-dose, and at 15, 30 min, 1, 2, 4, 8, 12 h post-dose.

On Day 2, at 24 h post-dose.

Day 3, at 48 h post-dose and at Follow-up.

Notes:

[27] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21 ^[28]	23	24	
Units: subjects				
SBP change > 20 mmHg	1	2	1	
SBP change < -20 mmHg	5	4	2	
DBP change > 10 mmHg	1	2	2	
DBP change < -10 mmHg	12	10	5	

Notes:

[28] - Safety population was used for the analysis of each group.

Statistical analyses

No statistical analyses for this end point

Primary: 13_Part 3 - Heart rate (0-24h) - Single dose - Subjects with COPD - Change from baseline

End point title	13_Part 3 - Heart rate (0-24h) - Single dose - Subjects with COPD - Change from baseline
End point description:	
Part 3 - Heart rate (0-24h) - Single dose - Subjects with COPD - Change from baseline.	
Data were derived from measurements using 12-lead ECG, extracted from 24 h Holter monitoring.	
Baseline is defined as the average HR of the 24 hours preceding the study drug administration on Day 1 of each treatment period.	
Results show the value obtained as adjusted mean and 95% CI.	
Presented are values extracted from Holter at pre-defined timepoints.	
The number of subjects contributing to the data is indicated (subjects receiving CHF 6366, Anoro, Placebo).	
End point type	Primary
End point timeframe:	
24h Holter ECG recording.	

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21 ^[29]	22	24	
Units: bpm				
arithmetic mean (confidence interval 95%)	1.6 (0.4 to 2.8)	-1.5 (-2.6 to -0.3)	-0.0 (-1.1 to 1.0)	

Notes:

[29] - Safety population was used for the analysis of each group.

Statistical analyses

Statistical analysis title	1_CHF 6366 vs Placebo
Statistical analysis description:	
Adjusted mean difference and 90% CI based on a linear model with terms for treatment, period and subject as fixed effects and Baseline value as a covariate.	
The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).	
Comparison groups	Part 3 - Subjects with COPD - CHF 6366, 240 µg v Part 3 - Subjects with COPD - Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other ^[30]
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.3
upper limit	3

Notes:

[30] - Model was carried out to estimate CIs.

Statistical analysis title	2_Anoro vs Placebo
Statistical analysis description:	
Adjusted mean difference and 90% CI based on a linear model with terms for treatment, period and subject as fixed effects and Baseline value as a covariate.	
The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=22 (cross-over study design).	
Comparison groups	Part 3 - Subjects with COPD - Anoro, 55/22 µg v Part 3 - Subjects with COPD - Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other ^[31]
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.7
upper limit	-0.1

Notes:

[31] - Model was carried out to estimate CIs.

Primary: 14_Part 3 - QTcF - Single dose - Subjects with COPD - Any post-dose timepoint

End point title	14_Part 3 - QTcF - Single dose - Subjects with COPD - Any post-dose timepoint ^[32]
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End point description:

Part 3 - QTcF - Single dose - Subjects with COPD - Any post-dose timepoint.

Data were derived from measurements using 12-lead ECG, extracted from 24 h Holter monitoring.

Baseline is defined as the time-matched measurement taken prior to the study drug administration on Day 1 of each treatment.

Presented are values extracted from Holter at pre-defined timepoints.

The number of subjects contributing to the data is indicated (subjects receiving CHF 6366, Anoro, Placebo).

End point type	Primary
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End point timeframe:

On Day 1, at pre-dose and 5, 15, 30 and 45 min and 1, 1.5, 2, 4, 8 and 12 h post-dose.

On Day 2, at 24 h post-dose.

Day 3, at 48 h post-dose and at Follow-up.

Notes:

[32] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21 ^[33]	22	24	
Units: subjects				
450 < QTcF ≤ 480 msec	0	0	1	
480 < QTcF ≤ 500 msec	0	0	0	
QTcF > 500 msec	0	0	0	
30 ≤ QTcF Increase from Baseline ≤ 60 msec	2	1	2	
QTcF Increase from Baseline > 60 msec	0	0	0	

Notes:

[33] - Safety population was used for the analysis of each group.

Statistical analyses

No statistical analyses for this end point

Primary: 15_Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1(0-24h)/24 h

End point title	15_Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1(0-24h)/24 h
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End point description:

Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1(0-24h)/24 h.

Data were derived from lung function measurements.

Results show the statistical comparison of FEV1(0-24h)/24 h for CHF 6366 vs Placebo, CHF 6366 vs Anoro, and Anoro vs Placebo.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (subjects receiving CHF 6366, Anoro, Placebo).

End point type	Primary
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End point timeframe:

On Day 1, at pre-dose and 15, 30 and 45 min and 1, 2, 6, 12, 23 and 24 h post-dose (Day 2).

On Day 3, and at Follow-up.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21 ^[34]	23	21	
Units: litre(s)				
arithmetic mean (confidence interval 95%)	1.498 (1.449 to 1.547)	1.617 (1.572 to 1.662)	1.350 (1.301 to 1.399)	

Notes:

[34] - Pharmacodynamic population was used for the analysis of each group.

Statistical analyses

Statistical analysis title	1_CHF 6366 vs Placebo
Statistical analysis description:	
Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.	
The value N=42, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).	
Comparison groups	Part 3 - Subjects with COPD - CHF 6366, 240 µg v Part 3 - Subjects with COPD - Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other ^[35]
Parameter estimate	Mean difference (final values)
Point estimate	0.1478
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07913
upper limit	0.2165

Notes:

[35] - Model was carried out to estimate CIs.

Statistical analysis title	2_CHF 6366 vs Anoro
Statistical analysis description:	
Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.	
The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=23 (cross-over study design).	
Comparison groups	Part 3 - Subjects with COPD - Anoro, 55/22 µg v Part 3 - Subjects with COPD - CHF 6366, 240 µg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other ^[36]
Parameter estimate	Mean difference (final values)
Point estimate	-0.1188
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1853
upper limit	-0.05235

Notes:

[36] - Model was carried out to estimate CIs.

Statistical analysis title	3_Anoro vs Placebo
Statistical analysis description:	
Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.	
The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).	
Comparison groups	Part 3 - Subjects with COPD - Anoro, 55/22 µg v Part 3 - Subjects with COPD - Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other ^[37]
Parameter estimate	Mean difference (final values)
Point estimate	0.2666
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2002
upper limit	0.3331

Notes:

[37] - Model was carried out to estimate CIs.

Primary: 16_Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1 Through

End point title	16_Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1 Through
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End point description:

Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1 Through.

Data were derived from lung function measurements.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (subjects receiving CHF 6366, Anoro, Placebo).

End point type	Primary
----------------	---------

End point timeframe:

On Day 1 at pre-dose and 15, 30 and 45 min and at 1, 2, 6, 12, 23 and 24 h post-dose (Day 2).

On Day 3 and at Follow-up.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21 ^[38]	23	22	
Units: litre(s)				
arithmetic mean (confidence interval 95%)	1.397 (1.344 to 1.451)	1.597 (1.548 to 1.646)	1.350 (1.299 to 1.402)	

Notes:

[38] - Pharmacodynamic population was used for the analysis of each group.

Statistical analyses

Statistical analysis title	1_CHF 6366 vs Placebo
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Statistical analysis description:

Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.

The value N=43, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).

Comparison groups	Part 3 - Subjects with COPD - CHF 6366, 240 µg v Part 3 - Subjects with COPD - Placebo
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Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other ^[39]
Parameter estimate	Mean difference (final values)
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.121

Notes:

[39] - Model was carried out to estimate CIs.

Statistical analysis title	2_CHF 6366 vs Anoro
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Statistical analysis description:

Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.

The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).

Comparison groups	Part 3 - Subjects with COPD - CHF 6366, 240 µg v Part 3 - Subjects with COPD - Anoro, 55/22 µg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other ^[40]
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.273
upper limit	-0.127

Notes:

[40] - Model was carried out to estimate CIs.

Statistical analysis title	3_Anoro vs Placebo
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Statistical analysis description:

Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.

The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).

Comparison groups	Part 3 - Subjects with COPD - Anoro, 55/22 µg v Part 3 - Subjects with COPD - Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other ^[41]
Parameter estimate	Mean difference (final values)
Point estimate	0.247

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.175
upper limit	0.318

Notes:

[41] - Model was carried out to estimate CIs.

Primary: 17_Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1 Peak

End point title	17_Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1 Peak
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End point description:

Part 3 - FEV1 - Single dose - Subjects with COPD - FEV1 Peak.

Data were derived from lung function measurements.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (subjects receiving CHF 6366, Anoro, Placebo).

End point type	Primary
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End point timeframe:

On Day 1 at pre-dose and 15, 30 and 45 min and at 1, 2, 6, 12, 23 and 24 h post-dose (Day 2).

On Day 3 and at Follow-up.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21 ^[42]	23	22	
Units: litre(s)				
arithmetic mean (confidence interval 95%)	1.740 (1.682 to 1.798)	1.743 (1.690 to 1.795)	1.478 (1.422 to 1.534)	

Notes:

[42] - Pharmacodynamic population was used for the analysis of each group.

Statistical analyses

Statistical analysis title	1_CHF 6366 vs Placebo
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Statistical analysis description:

Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.

The value N=43, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).

Comparison groups	Part 3 - Subjects with COPD - CHF 6366, 240 µg v Part 3 - Subjects with COPD - Placebo
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Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other ^[43]
Parameter estimate	Mean difference (final values)
Point estimate	0.262
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.183
upper limit	0.341

Notes:

[43] - Model was carried out to estimate CIs.

Statistical analysis title	2_CHF 6366 vs Anoro
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Statistical analysis description:

Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.

The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).

Comparison groups	Part 3 - Subjects with COPD - CHF 6366, 240 µg v Part 3 - Subjects with COPD - Anoro, 55/22 µg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other ^[44]
Parameter estimate	Mean difference (final values)
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.075

Notes:

[44] - Model was carried out to estimate CIs.

Statistical analysis title	3_Anoro vs Placebo
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Statistical analysis description:

Results are based on an analysis of covariance model with treatment, period, and subject as fixed effects and corresponding Baseline value (Day 1 pre dose FEV1 value of each period) as a covariate.

The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system. The correct value for subjects in the analysis is N=21 (cross-over study design).

Comparison groups	Part 3 - Subjects with COPD - Anoro, 55/22 µg v Part 3 - Subjects with COPD - Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other ^[45]
P-value	< 0.0001
Method	CHF pls specify method
Parameter estimate	Mean difference (final values)
Point estimate	0.265

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.188
upper limit	0.341

Notes:

[45] - Model was carried out to estimate CIs.

Primary: 18_Part 3 - FEV1 - Single dose - Subjects with COPD - Decrease from baseline \geq 20%

End point title	18_Part 3 - FEV1 - Single dose - Subjects with COPD - Decrease from baseline \geq 20% ^[46]
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End point description:

FEV1 - Single dose - Subjects with COPD - Decrease from baseline \geq 20% by scheduled time by treatment

Data were derived from lung function measurements.

Presented are representative results of the time points.

The number of subjects contributing to the data is indicated (subjects receiving CHF 6366, Anoro, Placebo).

End point type	Primary
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End point timeframe:

On Day 1 at pre-dose and 15, 30 and 45 min and at 1, 2, 6, 12, 23 and 24 h post-dose (Day 2).

On Day 3 and at Follow-up.

Notes:

[46] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical evaluation was performed.

The focus of the primary end points was safety.

Evaluation of the safety data was done descriptively.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21 ^[47]	23	24 ^[48]	
Units: subjects				
15 min	0	0	1	
30 min	0	0	1	
45 min	0	0	1	
1 h	0	0	1	
2 h	0	0	1	
6 h	0	0	0	

Notes:

[47] -

N=21

N=19

N=21

N=21

N=21

N=21

[48] -

N=23

N=23

N=23

N=24

Statistical analyses

No statistical analyses for this end point

Secondary: 19_Part 1 - Tmax - Single ascending dose - Healthy subjects

End point title	19_Part 1 - Tmax - Single ascending dose - Healthy subjects
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End point description:

Part 1 - Tmax - Single ascending dose - Healthy subjects.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

On Day 1, at pre-dose, 5, 10, 15, 30 and 45 mi, at 1, 1.5, 2, 4, 6, 8, 12, and 18 h post-dose.

On Day 2, at 24 h post-dose.

On Day 3, at 48 h post-dose.

End point values	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg	Part 1 - Healthy subjects - CHF 6366, 40 µg	Part 1 - Healthy subjects - CHF 6366, 80 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3 ^[49]	6	8	7
Units: hour				
median (full range (min-max))				
CHF 6361	1.0000 (0.933 to 1.017)	0.8750 (0.500 to 1.00)	1.0000 (0.750 to 1.000)	0.7500 (0.500 to 1.500)

Notes:

[49] - Pharmacokinetic population was used for the analysis of each group.

End point values	Part 1 - Healthy subjects - CHF 6366, 160 µg	Part 1 - Healthy subjects - CHF 6366, 360 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8 ^[50]	8 ^[51]		
Units: hour				
median (full range (min-max))				
CHF 6361	0.8835 (0.500 to 1.600)	1.1335 (0.733 to 1.500)		

Notes:

[50] - Results for Tmax:

CHF 6366: ND

CHF 6387: N=5; 0.7500 (0.750 – 1.000) h

[51] - Results for Tmax:

CHF 6366: N=3; 0.5000 (0.500 – 1.017) h

CHF 6387: N=8; 1.5085 (1.017 – 8.000) h

Statistical analyses

No statistical analyses for this end point

Secondary: 20_Part 1 - T1/2 - Single ascending dose - Healthy subjects

End point title	20_Part 1 - T1/2 - Single ascending dose - Healthy subjects
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End point description:

Part 1 - T1/2 - Single ascending dose - Healthy subjects.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

On Day 1, at pre-dose, 5, 10, 15, 30 and 45 mi, at 1, 1.5, 2, 4, 6, 8, 12, and 18 h post-dose.

On Day 2, at 24 h post-dose.

On Day 3, at 48 h post-dose.

End point values	Part 1 - Healthy subjects - CHF 6366, 40 µg	Part 1 - Healthy subjects - CHF 6366, 80 µg	Part 1 - Healthy subjects - CHF 6366, 160 µg	Part 1 - Healthy subjects - CHF 6366, 360 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4 ^[52]	7	3	7 ^[53]
Units: hour				
geometric mean (geometric coefficient of variation)				
CHF 6361	2.071 (± 25.39)	8.139 (± 152.2)	6.710 (± 132.2)	31.46 (± 23.38)

Notes:

[52] - Pharmacokinetic population was used for the analysis of each group.

[53] - Results for T1/2:

CHF 6366: ND

CHF 6387: N=2; 2.460 (0.5749) h

Statistical analyses

No statistical analyses for this end point

Secondary: 21_Part 1 - Cmax - Single ascending dose - Healthy subjects

End point title	21_Part 1 - Cmax - Single ascending dose - Healthy subjects
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End point description:

Part 1 - Cmax - Single ascending dose - Healthy subjects.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

On Day 1, at pre-dose, 5, 10, 15, 30 and 45 mi, at 1, 1.5, 2, 4, 6, 8, 12, and 18 h post-dose.

On Day 2, at 24 h post-dose.

On Day 3, at 48 h post-dose.

End point values	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg	Part 1 - Healthy subjects - CHF 6366, 40 µg	Part 1 - Healthy subjects - CHF 6366, 80 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3 ^[54]	6	8	7
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
CHF 6361	10.30 (± 26.73)	7.821 (± 31.12)	18.43 (± 23.70)	32.30 (± 49.51)

Notes:

[54] - Pharmacokinetic population was used for the analysis of each group.

End point values	Part 1 - Healthy subjects - CHF 6366, 160 µg	Part 1 - Healthy subjects - CHF 6366, 360 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8 ^[55]	8 ^[56]		
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
CHF 6361	67.57 (± 40.21)	167.3 (± 38.42)		

Notes:

[55] -

Results for Cmax:

CHF 6366: ND

CHF 6387: N=5; 29.95 (7.380) pg/mL

[56] -

Results for Cmax:

CHF 6366: N=3; 6.995 (10.38) pg/mL

CHF 6387: N=8; 61.08 (48.58) pg/mL

Statistical analyses

No statistical analyses for this end point

Secondary: 22_Part 1 - AUC(0-last) - Single ascending dose - Healthy subjects

End point title	22_Part 1 - AUC(0-last) - Single ascending dose - Healthy subjects
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End point description:

Part 1 - AUC(0-last) - Single ascending dose - Healthy subjects.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

On Day 1, at pre-dose, 5, 10, 15, 30 and 45 mi, at 1, 1.5, 2, 4, 6, 8, 12, and 18 h post-dose.

On Day 2, at 24 h post-dose.

On Day 3, at 48 h post-dose.

End point values	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg	Part 1 - Healthy subjects - CHF 6366, 40 µg	Part 1 - Healthy subjects - CHF 6366, 80 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3 ^[57]	5	8	7
Units: pg·h/mL				
geometric mean (geometric coefficient of variation)				
CHF 6361	12.31 (± 55.32)	8.678 (± 38.03)	38.17 (± 64.95)	108.7 (± 62.67)

Notes:

[57] - Pharmacokinetic population was used for the analysis of each group.

End point values	Part 1 - Healthy subjects - CHF 6366, 160 µg	Part 1 - Healthy subjects - CHF 6366, 360 µg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8 ^[58]	8 ^[59]		
Units: pg·h/mL				
geometric mean (geometric coefficient of variation)				
CHF 6361	270.8 (± 56.56)	1023 (± 27.99)		

Notes:

[58] - For AUC(0-last) pg·h/mL

CHF 6366: ND

CHF 6387: N=2; 24.08 (53.36)

[59] -
For AUC(0-last) pg·h/mL
CHF 6366: ND
CHF 6387: N=8; 141.2 (95.35)

Statistical analyses

No statistical analyses for this end point

Secondary: 23_Part 2 - Tmax - Multiple ascending dose - Subjects with asthma - Day 1

End point title	23_Part 2 - Tmax - Multiple ascending dose - Subjects with asthma - Day 1
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End point description:

Part 2 - Tmax - Multiple ascending dose - Subjects with asthma.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12 h post-dose.

Day 2, 18 h post-Day 1 dose.

Day 2 to Day 6 pre-dose.

Day 7, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12, 18 h post-dose.

Day 8 at 24 h post-dose.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[60]	9	9 ^[61]	9
Units: hour				
median (full range (min-max))				
CHF 6361	0.7500 (0.500 to 1.067)	1.0000 (0.500 to 1.500)	1.0000 (0.733 to 1.500)	1.0000 (0.750 to 1.500)

Notes:

[60] - Pharmacokinetic population was used for the analysis of each group.

[61] -

For Tmax hour

CHF 6366: ND

CHF 6387: N=3; 1.0000 (0.500 - 1.500)

Statistical analyses

No statistical analyses for this end point

Secondary: 24_Part 2 - T1/2 - Multiple ascending dose - Subjects with asthma - Day 1

End point title	24_Part 2 - T1/2 - Multiple ascending dose - Subjects with asthma - Day 1
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End point description:

Part 2 - T1/2 - Multiple ascending dose - Subjects with asthma.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12 h post-dose.

Day 2, 18 h post-Day 1 dose.

Day 2 to Day 6 pre-dose.

Day 7, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12, 18 h post-dose.

Day 8 at 24 h post-dose.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5 ^[62]	5	5	5
Units: hour				
geometric mean (geometric coefficient of variation)				
CHF 6361	1.685 (± 23.87)	2.648 (± 53.19)	6.886 (± 96.15)	11.04 (± 65.67)

Notes:

[62] - Pharmacokinetic population was used for the analysis of each group.

Statistical analyses

No statistical analyses for this end point

Secondary: 25_Part 2 - Cmax - Multiple ascending dose - Subjects with asthma - Day 1

End point title	25_Part 2 - Cmax - Multiple ascending dose - Subjects with asthma - Day 1
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End point description:

Part 2 - Cmax - Multiple ascending dose - Subjects with asthma - Day 1.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the

plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
End point timeframe:	
Day 1, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12 h post-dose.	
Day 2, 18 h post-Day 1 dose.	
Day 2 to Day 6 pre-dose.	
Day 7, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12, 18 h post-dose.	
Day 8 at 24 h post-dose.	

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[63]	9	9 ^[64]	9
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
CHF 6361	14.08 (± 39.98)	26.24 (± 74.53)	54.79 (± 77.85)	43.60 (± 52.97)

Notes:

[63] - Pharmacokinetic population was used for the analysis of each group.

[64] -

For Cmax pg/mL

CHF 6366: ND

CHF 6387: N=3; 31.34 (16.86)

Statistical analyses

No statistical analyses for this end point

Secondary: 26_Part 2 - AUC(0-last) - Multiple ascending dose - Subjects with asthma - Day 1

End point title	26_Part 2 - AUC(0-last) - Multiple ascending dose - Subjects with asthma - Day 1
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End point description:

Part 2 - AUC(0-last) - Multiple ascending dose - Subjects with asthma.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
End point timeframe:	
Day 1, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12 h post-dose.	
Day 2, 18 h post-Day 1 dose.	

Day 2 to Day 6 pre-dose.
Day 7, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12, 18 h post-dose.
Day 8 at 24 h post-dose.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8 ^[65]	9	9 ^[66]	9
Units: pg·h/mL				
geometric mean (geometric coefficient of variation)				
CHF 6361	23.03 (± 71.85)	60.92 (± 141.8)	241.4 (± 121.2)	208.2 (± 80.49)

Notes:

[65] - Pharmacokinetic population was used for the analysis of each group.

[66] -

For AUC(0-last) pg·h/mL

CHF 6366: ND

CHF 6387: N=3; 14.80 (189.8)

Statistical analyses

No statistical analyses for this end point

Secondary: 27_Part 2 - Tmax - Multiple ascending dose - Subjects with asthma - Day 7

End point title	27_Part 2 - Tmax - Multiple ascending dose - Subjects with asthma - Day 7
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End point description:

Part 2 - Tmax - Multiple ascending dose - Subjects with asthma - Day 7.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12 h post-dose.

Day 2, 18 h post-Day 1 dose.

Day 2 to Day 6 pre-dose.

Day 7, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12, 18 h post-dose.

Day 8 at 24 h post-dose.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6 ^[67]	8	9 ^[68]	8 ^[69]
Units: hour				
median (full range (min-max))				
CHF 6361	0.8750 (0.750 to 1.517)	0.8750 (0.517 to 1.000)	1.0000 (0.500 to 1.533)	1.0165 (0.750 to 2.000)

Notes:

[67] - Pharmacokinetic population was used for the analysis of each group.

[68] -

For Tmax hour

CHF 6366: ND

CHF 6387: N=5; 0.7500 (0.500 - 1.000)

[69] -

For Tmax hour

CHF 6366: ND

CHF 6387: N=5; 1.0000 (0.750 - 2.000)

Statistical analyses

No statistical analyses for this end point

Secondary: 28_Part 2 - T1/2 - Multiple ascending dose - Subjects with asthma - Day 7

End point title	28_Part 2 - T1/2 - Multiple ascending dose - Subjects with asthma - Day 7
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End point description:

Part 2 - T1/2 - Multiple ascending dose - Subjects with asthma - Day 7.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12 h post-dose.

Day 2, 18 h post-Day 1 dose.

Day 2 to Day 6 pre-dose.

Day 7, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12, 18 h post-dose.

Day 8 at 24 h post-dose.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5 ^[70]	5	3	8
Units: hour				
geometric mean (geometric coefficient of variation)				
CHF 6361	3.130 (± 56.85)	7.964 (± 91.13)	16.63 (± 37.01)	24.05 (± 71.54)

Notes:

[70] - Pharmacokinetic population was used for the analysis of each group.

Statistical analyses

No statistical analyses for this end point

Secondary: 29_Part 2 - Cmax - Multiple ascending dose - Subjects with asthma - Day 7

End point title	29_Part 2 - Cmax - Multiple ascending dose - Subjects with asthma - Day 7
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End point description:

Part 2 - Cmax - Multiple ascending dose - Subjects with asthma - Day 7.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12 h post-dose.

Day 2, 18 h post-Day 1 dose.

Day 2 to Day 6 pre-dose.

Day 7, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12, 18 h post-dose.

Day 8 at 24 h post-dose.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6 ^[71]	8	9 ^[72]	8 ^[73]
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
CHF 6361	12.93 (± 21.22)	27.13 (± 87.00)	65.48 (± 52.35)	78.98 (± 49.70)

Notes:

[71] - Pharmacokinetic population was used for the analysis of each group.

[72] -

For C_{max} pg/mL

CHF 6366: ND

CHF 6387: N=5; 32.59 (22.77)

[73] -

For C_{max} pg/mL

CHF 6366: ND

CHF 6387: N=5; 38.44 (24.56)

Statistical analyses

No statistical analyses for this end point

Secondary: 30_Part 2 - AUC(0-last) - Multiple ascending dose - Subjects with asthma - Day 7

End point title	30_Part 2 - AUC(0-last) - Multiple ascending dose - Subjects with asthma - Day 7
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End point description:

Part 2 - AUC(0-last) - Multiple ascending dose - Subjects with asthma - Day 7.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12 h post-dose.

Day 2, 18 h post-Day 1 dose.

Day 2 to Day 6 pre-dose.

Day 7, pre-dose and 5, 10, 15, 30 and 45 min, 1, 1.5, 2, 4, 6, 8, 12, 18 h post-dose.

Day 8 at 24 h post-dose.

End point values	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg	Part 2 - Subjects with asthma - CHF 6366, 240 µg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7 ^[74]	8	9 ^[75]	9 ^[76]
Units: pg·h/mL				
geometric mean (geometric coefficient of variation)				
CHF 6361	30.55 (± 70.10)	147.0 (± 146.4)	463.2 (± 57.7)	618.5 (± 50.05)

Notes:

[74] - Pharmacokinetic population was used for the analysis of each group.

[75] -

For AUC(0-last) pg·h/mL

CHF 6366: ND
CHF 6387: N=5; 17.75 (167.9)

[76] -
For AUC(0-last) pg·h/mL
CHF 6366: ND
CHF 6387: N=6; 36.85 (228.4)

Statistical analyses

No statistical analyses for this end point

Secondary: 31_Part 3 - Tmax - Single dose - Subjects with COPD

End point title	31_Part 3 - Tmax - Single dose - Subjects with COPD
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End point description:

Part 3 - Tmax - Single dose - Subjects with COPD.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, at pre-dose and 5, 10, 15, 30 and 45 min, at 1, 1.5, 2, 4, 6, 8, 12, and 18 h.

Day 2, at 24 h post-dose.

Day 3, at 48 h post-dose.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	3 ^[77]			
Units: hour				
median (full range (min-max))				
CHF 6366	0.1830 (0.167 to 0.250)			
CHF 6387	1.0330 (0.750 to 2.033)			
CHF 6361	1.0000 (0.500 to 2.000)			

Notes:

[77] - Pharmacokinetic population was used for the analysis of each group.

N=3

N=5

N=20

Statistical analyses

No statistical analyses for this end point

Secondary: 32_Part 3 - T1/2 - Single dose - Subjects with COPD

End point title	32_Part 3 - T1/2 - Single dose - Subjects with COPD
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End point description:

Part 3 - T1/2 - Single dose - Subjects with COPD.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, at pre-dose and 5, 10, 15, 30 and 45 min, at 1, 1.5, 2, 4, 6, 8, 12, and 18 h.

Day 2, at 24 h post-dose.

Day 3, at 48 h post-dose.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	17 ^[78]			
Units: hour				
geometric mean (geometric coefficient of variation)				
CHF 6361	4.608 (± 94.25)			

Notes:

[78] - Pharmacokinetic population was used for the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: 33_Part 3 - Cmax - Single dose - Subjects with COPD

End point title	33_Part 3 - Cmax - Single dose - Subjects with COPD
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End point description:

Part 3 - Cmax - Single dose - Subjects with COPD.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
End point timeframe:	
Day 1, at pre-dose and 5, 10, 15, 30 and 45 min, at 1, 1.5, 2, 4, 6, 8, 12, and 18 h.	
Day 2, at 24 h post-dose.	
Day 3, at 48 h post-dose.	

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	3 ^[79]			
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
CHF 6366	7.167 (± 18.55)			
CHF 6387	31.89 (± 23.88)			
CHF 6361	48.86 (± 47.26)			

Notes:

[79] - Pharmacokinetic population was used for the analysis of each group.

N=3

N=5

N=20

Statistical analyses

No statistical analyses for this end point

Secondary: 34_Part 3 - AUC(0-last) - Single dose - Subjects with COPD

End point title	34_Part 3 - AUC(0-last) - Single dose - Subjects with COPD
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End point description:

Part 3 - AUC(0-last) - Single dose - Subjects with COPD.

Citrated blood was collected for PK assessment (in plasma) occurred at the specified time points.

Results show data for PK parameters of CHF 6366 (parent compound) and its metabolites CHF 6387 and CHF 6361. For some of the PK parameters (when low concentration of CHF 6366 was administered), the plasma concentration of the parent compound CHF 6366 and of the metabolite CHF 6387 was not determined. This was because the plasma concentration was 'Below the limit of quantification' (BLQ). Available data for the parent compound and metabolites CHF 6387, are shown in the footnotes of the results table.

The number of subjects contributing to the data is indicated.

End point type	Secondary
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End point timeframe:

Day 1, at pre-dose and 5, 10, 15, 30 and 45 min, at 1, 1.5, 2, 4, 6, 8, 12, and 18 h.

Day 2, at 24 h post-dose.

Day 3, at 48 h post-dose.

End point values	Part 3 - Subjects with COPD - CHF 6366, 240 µg			
Subject group type	Subject analysis set			
Number of subjects analysed	2 ^[80]			
Units: pg·h/mL				
geometric mean (geometric coefficient of variation)				
CHF 6387	35.87 (± 78.31)			
CHF 6361	198.2 (± 73.67)			

Notes:

[80] - Pharmacokinetic population was used for the analysis of each group.

N=2

N=21

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from the time of the patient informed consent signature up to the study completion or discontinuation. For all study parts, a follow-up visit was between 7 to 14 days after the last dose administration.

Adverse event reporting additional description:

Safety population was used for the evaluation of AE (shown as TEAEs).

Safety population: all randomised subjects who received at least one dose of study treatment.

TEAEs: AEs starting on or after the first dose of study drug administration, but on or before date of last dose of study drug +7 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Part 1 - Healthy subjects - CHF 6366, 5 µg
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Reporting group description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 5 µg.

Reporting group title	Part 1 - Healthy subjects - CHF 6366, 10 µg
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Reporting group description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 10 µg.

Reporting group title	Part 1 - Healthy subjects - CHF 6366, 20 µg
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Reporting group description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 20 µg.

Reporting group title	Part 1 - Healthy subjects - CHF 6366, 40 µg
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Reporting group description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 40 µg.

Reporting group title	Part 1 - Healthy subjects - CHF 6366, 80 µg
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Reporting group description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 80 µg.

Reporting group title	Part 1 - Healthy subjects - CHF 6366, 160 µg
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Reporting group description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 160 µg.

Reporting group title	Part 1 - Healthy subjects - CHF 6366, 360 µg
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Reporting group description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, 360 µg.

Reporting group title	Part 1 - Healthy subjects - Placebo
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Reporting group description:

Part 1 of the study.

Healthy subjects who received placebo.

Reporting group title	Part 1 - Healthy subjects - CHF 6366, any dose
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Reporting group description:

Part 1 of the study.

Healthy subjects who received a single ascending dose of CHF 6366, any dose.

Reporting group title	Part 2 - Subjects with asthma - CHF 6366, 40 µg
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Reporting group description:

Part 2 of the study.

Subjects with asthma who received multiple ascending dose of CHF 6366, 40 µg for 7 days, according to the escalation scheme.

Reporting group title	Part 2 - Subjects with asthma - CHF 6366, 80 µg
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Reporting group description:

Part 2 of the study.

Subjects with asthma who received multiple ascending dose of CHF 6366, 80 µg for 7 days, according to the escalation scheme.

Reporting group title	Part 2 - Subjects with asthma - CHF 6366, 160 µg
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Reporting group description:

Part 2 of the study.

Subjects with asthma who received multiple ascending dose of CHF 6366, 160 µg for 7 days, according to the escalation scheme.

Reporting group title	Part 2 - Subjects with asthma - CHF 6366, 240 µg
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Reporting group description:

Part 2 of the study.

Subjects with asthma who received multiple ascending dose of CHF 6366, 240 µg for 7 days, according to the escalation scheme.

Reporting group title	Part 2 - Subjects with asthma - Placebo
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Reporting group description:

Part 2 of the study.

Subjects with asthma who received placebo for 7 days.

Reporting group title	Part 3 - Subjects with COPD - CHF 6366, 240 µg
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Reporting group description:

Part 3 of the study.

Subjects with COPD, who received a single-dose of CHF 6366, 240 µg, according to a randomised, placebo-controlled, active-controlled*, 3-way cross-over design.

*The active control was Anoro [Anoro Ellipta (umeclidinium and vilanterol dry powder inhaler, 55/22 µg)].

Reporting group title	Part 3 - Subjects with COPD - Anoro, 55/22 µg
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Reporting group description:

Part 3 of the study.

Subjects with COPD, who received a single-dose of Anoro*, according to a randomised, placebo-controlled, active-controlled*, 3-way cross-over design.

*The active control was Anoro [Anoro Ellipta (umeclidinium and vilanterol dry powder inhaler, 55/22 µg)].

Reporting group title	Part 3 - Subjects with COPD - Placebo
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Reporting group description:

Part 3 of the study.

Subjects with COPD, who received a single-dose of placebo, according to a randomised, placebo-

controlled, active-controlled*, 3-way cross-over design.

*The active control was Anoro [Anoro Ellipta (umeclidinium and vilanterol dry powder inhaler, 55/22 µg)].

Reporting group title	Part 3 - Subjects with COPD - Overall
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Reporting group description:

Part 3 of the study.

Subjects with COPD - overall summary.

Subjects received a single-dose of the 3 treatments CHF 6366 (240 µg), Anoro*, according to a randomised, and placebo-controlled, active-controlled*, 3-way cross-over design.

*The active control was Anoro [Anoro Ellipta (umeclidinium and vilanterol dry powder inhaler, 55/22 µg)].

Serious adverse events	Part 1 - Healthy subjects - CHF 6366, 5 µg	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Part 1 - Healthy subjects - CHF 6366, 40 µg	Part 1 - Healthy subjects - CHF 6366, 80 µg	Part 1 - Healthy subjects - CHF 6366, 160 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Part 1 - Healthy subjects - CHF 6366, 360 µg	Part 1 - Healthy subjects - Placebo	Part 1 - Healthy subjects - CHF 6366, any dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events			
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Serious adverse events	Part 2 - Subjects with asthma - CHF 6366, 240 µg	Part 2 - Subjects with asthma - Placebo	Part 3 - Subjects with COPD - CHF 6366, 240 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	Part 3 - Subjects with COPD - Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Part 1 - Healthy subjects - CHF 6366, 5 µg	Part 1 - Healthy subjects - CHF 6366, 10 µg	Part 1 - Healthy subjects - CHF 6366, 20 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	2 / 8 (25.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Infusion site bruising			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Medical device site reaction	Additional description: AE was due to the Holter device electrode patch.		
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Application site dermatitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Puncture site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nipple pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Investigations			
Chlamydia test positive			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood urine present			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ear injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Photopsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 1 - Healthy subjects - CHF 6366, 40 µg	Part 1 - Healthy subjects - CHF 6366, 80 µg	Part 1 - Healthy subjects - CHF 6366, 160 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	2 / 8 (25.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Infusion site bruising			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Medical device site reaction	Additional description: AE was due to the Holter device electrode patch.		

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Application site dermatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Puncture site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nipple pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Investigations			
Chlamydia test positive			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood urine present			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ear injury			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Skin abrasion subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	1 / 8 (12.50%) 1
Dizziness subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Dizziness postural subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Lethargy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Eye disorders Photopsia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Haematochezia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0
Gingival pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 1 - Healthy subjects - CHF 6366, 360 µg	Part 1 - Healthy subjects - Placebo	Part 1 - Healthy subjects - CHF 6366, any dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	9 / 24 (37.50%)	9 / 30 (30.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Infusion site bruising			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	1 / 30 (3.33%) 1
Medical device site reaction	Additional description: AE was due to the Holter device electrode patch.		
subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	2 / 24 (8.33%) 2	4 / 30 (13.33%) 4
Application site dermatitis			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Chest discomfort			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Puncture site pain			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Feeling hot			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Pyrexia			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Immune system disorders			
Food allergy			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Dysmenorrhoea			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Nipple pain			
subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)	2 / 24 (8.33%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	3 / 24 (12.50%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Investigations			
Chlamydia test positive			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Blood urine present			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Contusion			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Ear injury subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Skin abrasion subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 24 (8.33%) 2	4 / 30 (13.33%) 5
Dizziness subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Dizziness postural subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Lethargy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Eye disorders Photopsia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 24 (4.17%) 1	0 / 30 (0.00%) 0
Haematochezia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 24 (4.17%) 1	0 / 30 (0.00%) 0
Aphthous ulcer			

subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 24 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 24 (4.17%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 24 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Infections and infestations Rhinitis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Diverticulitis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 24 (0.00%) 0	0 / 30 (0.00%) 0

Non-serious adverse events	Part 2 - Subjects with asthma - CHF 6366, 40 µg	Part 2 - Subjects with asthma - CHF 6366, 80 µg	Part 2 - Subjects with asthma - CHF 6366, 160 µg
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 9 (55.56%)	7 / 9 (77.78%)	5 / 9 (55.56%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Lipoma subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
General disorders and administration			

site conditions			
Infusion site bruising			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Medical device site reaction	Additional description: AE was due to the Holter device electrode patch.		
subjects affected / exposed	0 / 9 (0.00%)	6 / 9 (66.67%)	4 / 9 (44.44%)
occurrences (all)	0	6	4
Application site dermatitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Chest discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Puncture site pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast tenderness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nipple pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Investigations			
Chlamydia test positive			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Blood urine present			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Ear injury subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Skin abrasion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	1 / 9 (11.11%) 2
Dizziness subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	1 / 9 (11.11%) 1
Dizziness postural subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0
Lethargy subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Eye disorders Photopsia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0
Haematochezia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Arthralgia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Rhinitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2 - Subjects with asthma - CHF 6366, 240 µg	Part 2 - Subjects with asthma - Placebo	Part 3 - Subjects with COPD - CHF 6366, 240 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 9 (55.56%)	6 / 12 (50.00%)	9 / 21 (42.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Lipoma subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
General disorders and administration site conditions			
Infusion site bruising subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Medical device site reaction subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	4 / 12 (33.33%) 4	1 / 21 (4.76%) 1
Additional description: AE was due to the Holter device electrode patch.			
Application site dermatitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Chest discomfort subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Puncture site pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Feeling hot subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Immune system disorders			
Food allergy subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Reproductive system and breast disorders			
Breast tenderness subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0

Nipple pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Nasal congestion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	1 / 21 (4.76%) 1
Epistaxis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Throat irritation subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Investigations			
Chlamydia test positive subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Blood urine present subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Injury, poisoning and procedural			

complications			
Arthropod bite			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Ear injury			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 9 (22.22%)	1 / 12 (8.33%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Dizziness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Dizziness postural			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Photopsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Haematochezia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gingival pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Arthralgia			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Infections and infestations			
Rhinitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Diverticulitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0

Non-serious adverse events	Part 3 - Subjects with COPD - Anoro, 55/22 µg	Part 3 - Subjects with COPD - Placebo	Part 3 - Subjects with COPD - Overall
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 23 (39.13%)	12 / 24 (50.00%)	19 / 24 (79.17%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Lipoma subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 24 (4.17%) 1	1 / 24 (4.17%) 1
General disorders and administration site conditions			
Infusion site bruising subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 24 (8.33%) 2	3 / 24 (12.50%) 3
Medical device site reaction subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 24 (8.33%) 2	4 / 24 (16.67%) 5
Application site dermatitis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Chest discomfort subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Puncture site pain subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Feeling hot subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 24 (4.17%) 1	1 / 24 (4.17%) 1
Pyrexia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
Immune system disorders			
Food allergy subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
Reproductive system and breast disorders			
Breast tenderness subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0

Additional description: AE was due to the Holter device electrode patch.

Nipple pain subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2	2 / 24 (8.33%) 2	4 / 24 (16.67%) 5
Nasal congestion subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	3 / 24 (12.50%) 3	4 / 24 (16.67%) 5
Epistaxis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Throat irritation subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 24 (4.17%) 1	3 / 24 (12.50%) 3
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 24 (8.33%) 2	2 / 24 (8.33%) 2
Investigations			
Chlamydia test positive subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Blood urine present subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
Injury, poisoning and procedural			

complications			
Arthropod bite			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Ear injury			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 23 (13.04%)	2 / 24 (8.33%)	5 / 24 (20.83%)
occurrences (all)	4	2	7
Dizziness			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Dizziness postural			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Photopsia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

Haematochezia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gingival pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 23 (0.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Arthralgia			

subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	3 / 24 (12.50%) 3	3 / 24 (12.50%) 3
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
Infections and infestations			
Rhinitis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Sinusitis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	0 / 24 (0.00%) 0
Diverticulitis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 24 (0.00%) 0	1 / 24 (4.17%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2018	<p>1) New proposed maximum dose (360 µg/day) to be tested during the first part of the pH1 clinical trial is still supported by the preclinical data (Rat 4-week inhalation, Dog 4-week inhalation).</p> <p>2) An additional Cohort (Cohort H) has been included for testing the highest dosage planned in Part 1 (320 µg). As for Cohort A and B, 12 subjects will be randomized in a 2:1 ratio to active CHF 6366 SD7 (8 subjects) and placebo (4 subjects). Subjects can be recruited from the two previous Cohorts (A and B) or be new individuals, respecting the study inclusion and exclusion criteria.</p>

Notes:

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.

None.

Notes: