Clinical trial results:
A MULTICENTER, MULTINATIONAL, SINGLE-DOSE, OPEN LABEL, RANDOMIZED, 2-WAY CROSSOVER, CLINICAL PHARMACOLOGY STUDY OF CHF 1535 100/6 NEXT DPI® (FIXED COMBINATION OF BECLOMETHASONE DIPROPIONATE 100 µg PLUS FORMOTEROL FUMARATE 6 µg) VERSUS THE FREE COMBINATION OF LICENSED BECLOMETHASONE DPI AND FORMOTEROL DPI IN ASTHMATIC ADOLESCENTS AND ADULTS PATIENTS

Summary

EudraCT number	2010-018947-33
Trial protocol	GB DK
Global end of trial date	25 September 2011

Results information

Result version number	v1 (current)
This version publication date	11 July 2016
First version publication date	09 August 2015

Trial information

Trial identification

Sponsor protocol code	CCD-1017-PR-0034

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01191424
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 Manager, Chiesi Clinical Trials, Chiesi Farmaceutici SpA, ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency Manager, Chiesi Clinical Trials, Chiesi Farmaceutici SpA, ClinicalTrials_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000548-PIP01-09
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 September 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2011
Global end of trial reached?	Yes
Global end of trial date	25 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the systemic exposure to beclomethasone-17-monopropionate (B17MP; active metabolite of beclomethasone dipropionate [BDP]) as area under the plasma drug concentration-time curve calculated to the last quantifiable time point (AUC0-t), after 4 single inhalations of the fixed combination CHF 1535 100/6 NEXT DPI® (total dose: BDP 400 µg/formoterol fumarate 24 µg) in comparison with a free combination of BDP dry powder inhaler (DPI) and formoterol DPI licensed products in the asthmatic adolescent and adult patient populations.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Denmark: 28
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	28
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 33 adult patients from 1 study centre in the UK and 29 adolescents from 1 study centre in Denmark were screened in this 2-way cross over study. One adolescent and 3 adult patients failed screening: 28 adolescent and 30 adult patients were randomised.

Period 1

Period 1 title	Overall trial by sequence (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The treatment in this study was administered open-label, i.e., the investigator and patients knew the identity of the drug.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence T--R

Arm description:

Test Treatment (fixed combination): CHF 1535 100/6 NEXT DPI® 4 inhalations (total daily dose at the clinic: BDP 400 µg/FF 24 µg),

Reference Treatment (free combination): BDP 100 µg DPI 4 inhalations (Clenil® Pulvinal®, total daily dose at the clinic: 400 µg) + formoterol fumarate 12 µg DPI 2 inhalations (Foradil®Aerolizer®, total daily dose at the clinic: 24 µg).

Arm type	experimental - active comparator
Investigational medicinal product name	CHF 1535 NEXT DPI® - BDP DPI+FF DPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

No specific treatment was provided during the run-in period.
At the end of the run-in period, patients started the first 1-day treatment period (Visit 2) and were randomised to either TEST (CHF 1535 NEXT DPI® 100 + 6 µg) or REFERENCE (free combination of BDP DPI 100 µg plus formoterol DPI 12 µg) study treatment.
Prior to the next visit, patients underwent a 1- to 3-week wash-out period, before the next study treatment administration at Visit 3.
During the second 1-day treatment period (Visit 3), patients were assigned to the other study treatment according to the sequence specified in the randomisation list and the study cross-over design.

Arm title	Sequence R--T

Arm description:

Reference Treatment (free combination): BDP 100 µg DPI 4 inhalations (Clenil® Pulvinal®, total daily dose at the clinic: 400 µg) + formoterol fumarate 12 µg DPI 2 inhalations (Foradil®Aerolizer®, total daily dose at the clinic: 24 µg).
Test Treatment (fixed combination): CHF 1535 100/6 NEXT DPI® 4 inhalations (total daily dose at the clinic: BDP 400 µg/FF 24 µg)

Arm type	Active comparator - Experimental

Investigational medicinal product name	BDP+FF DPI - CHF1535 NEXT DPI
Investigational medicinal product code	
Other name	beclomethasone dipropionate, formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

No specific treatment was provided during the run-in period.
At the end of the run-in period, patients started the first 1-day treatment period (Visit 2) and were randomised to either TEST (CHF 1535 NEXT DPI® 100 + 6 µg) or REFERENCE (free combination of BDP DPI 100 µg plus formoterol DPI 12 µg) study treatment.
Prior to the next visit, patients underwent a 1- to 3-week wash-out period, before the next study treatment administration at Visit 3.
During the second 1-day treatment period (Visit 3), patients were assigned to the other study treatment according to the sequence specified in the randomisation list and the study cross-over design.

Number of subjects in period 1	Sequence T--R	Sequence R--T
Started	29	29
wash out	28	29
Completed	28	29
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Sequence T--R

Reporting group description:

Test Treatment (fixed combination): CHF 1535 100/6 NEXT DPI® 4 inhalations (total daily dose at the clinic: BDP 400 µg/FF 24 µg),

Reference Treatment (free combination): BDP 100 µg DPI 4 inhalations (Clenil® Pulvinal®, total daily dose at the clinic: 400 µg) + formoterol fumarate 12 µg DPI 2 inhalations (Foradil®Aerolizer®, total daily dose at the clinic: 24 µg).

Reporting group title	Sequence R--T

Reporting group description:

Reference Treatment (free combination): BDP 100 µg DPI 4 inhalations (Clenil® Pulvinal®, total daily dose at the clinic: 400 µg) + formoterol fumarate 12 µg DPI 2 inhalations (Foradil®Aerolizer®, total daily dose at the clinic: 24 µg).
Test Treatment (fixed combination): CHF 1535 100/6 NEXT DPI® 4 inhalations (total daily dose at the clinic: BDP 400 µg/FF 24 µg)

Reporting group values	Sequence T--R	Sequence R--T	Total
Number of subjects	29	29	58
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	14	14	28
Adults (18-64 years)	15	15	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	0	0	
standard deviation	± 0	± 0	-
Gender categorical Units: Subjects			
Female	13	13	26
Male	16	16	32

Subject analysis sets

Subject analysis set title	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

For PK/PD population is intended the subpopulation of the safety population without any major protocol deviation that could affect the PK/PD.

Subject analysis set title	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD

Subject analysis set type	Sub-group analysis

Subject analysis set description:

For PK/PD population is intended the subpopulation of the safety population without any major protocol deviation that could affect the PK/PD.

Subject analysis set title	BDP DPI + FF DPI treatment phase - Adults - PK/PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

For PK/PD population is intended the subpopulation of the safety population without any major protocol deviation that could affect the PK/PD.

Subject analysis set title	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

For PK/PD population is intended the subpopulation of the safety population without any major protocol deviation that could affect the PK/PD.

Subject analysis set title	CHF 1535 100/6 NEXT DPI treatment phase - Adults - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised adult subjects who used at least one dose of study medication.

Subject analysis set title	CHF 1535NEXT DPI treatment phase - Adolescents - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised adolescent subjects who used at least one dose of study medication.

Subject analysis set title	BDP DPI + FF DPI treatment phase - Adults - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised adult subjects who used at least one dose of study medication.

Subject analysis set title	BDP DPI + FF DPI treatment phase - Adolescents - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised adolescent subjects who used at least one dose of study medication.

Reporting group values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects	30	27	30
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	27	0
Adults (18-64 years)	30	0	30
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.6	13.7	37.6

standard deviation	± 10.8	± 1.7	± 9.7

Gender categorical Units: Subjects			
Female	13	12	13
Male	17	15	17

Reporting group values	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD	CHF 1535 100/6 NEXT DPI treatment phase - Adults - Safety	CHF 1535NEXT DPI treatment phase - Adolescents - Safety
Number of subjects	27	30	28
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	27	0	28
Adults (18-64 years)	0	30	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	14.1		
standard deviation	± 1.7	±	±
Gender categorical Units: Subjects			
Female	12	13	13
Male	15	17	15

Reporting group values	BDP DPI + FF DPI treatment phase - Adults - Safety	BDP DPI + FF DPI treatment phase - Adolescents - Safety	
Number of subjects	30	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	27	
Adults (18-64 years)	30	0	
From 65-84 years	0	0	
85 years and over	0	0	

Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female	13	12	
Male	17	15	

End points

End points reporting groups

Reporting group title	Sequence T--R

Reporting group description:

Test Treatment (fixed combination): CHF 1535 100/6 NEXT DPI® 4 inhalations (total daily dose at the clinic: BDP 400 µg/FF 24 µg),

Reference Treatment (free combination): BDP 100 µg DPI 4 inhalations (Clenil® Pulvinal®, total daily dose at the clinic: 400 µg) + formoterol fumarate 12 µg DPI 2 inhalations (Foradil®Aerolizer®, total daily dose at the clinic: 24 µg).

Reporting group title	Sequence R--T

Reporting group description:

Reference Treatment (free combination): BDP 100 µg DPI 4 inhalations (Clenil® Pulvinal®, total daily dose at the clinic: 400 µg) + formoterol fumarate 12 µg DPI 2 inhalations (Foradil®Aerolizer®, total daily dose at the clinic: 24 µg).
Test Treatment (fixed combination): CHF 1535 100/6 NEXT DPI® 4 inhalations (total daily dose at the clinic: BDP 400 µg/FF 24 µg)

Subject analysis set title	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

For PK/PD population is intended the subpopulation of the safety population without any major protocol deviation that could affect the PK/PD.

Subject analysis set title	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

For PK/PD population is intended the subpopulation of the safety population without any major protocol deviation that could affect the PK/PD.

Subject analysis set title	BDP DPI + FF DPI treatment phase - Adults - PK/PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

For PK/PD population is intended the subpopulation of the safety population without any major protocol deviation that could affect the PK/PD.

Subject analysis set title	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

For PK/PD population is intended the subpopulation of the safety population without any major protocol deviation that could affect the PK/PD.

Subject analysis set title	CHF 1535 100/6 NEXT DPI treatment phase - Adults - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised adult subjects who used at least one dose of study medication.

Subject analysis set title	CHF 1535NEXT DPI treatment phase - Adolescents - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised adolescent subjects who used at least one dose of study medication.

Subject analysis set title	BDP DPI + FF DPI treatment phase - Adults - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised adult subjects who used at least one dose of study medication.

Subject analysis set title	BDP DPI + FF DPI treatment phase - Adolescents - Safety

Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised adolescent subjects who used at least one dose of study medication.

Primary: Plasma AUC0-t for B17MP

End point title	Plasma AUC0-t for B17MP

End point description:

For the purpose of the primary endpoint analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

After single administration, the area under the plasma concentration versus time curve up to the last quantifiable concentration (AUC0-t) is used to measure the extent of absorption.

End point type	Primary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*hr/mL				
arithmetic mean (standard deviation)	2407.37 (± 562.9)	3396.37 (± 659.36)	2058.24 (± 523.38)	3115.96 (± 1452.69)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.101
upper limit	1.252

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v

	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.027
upper limit	1.276

Secondary: Plasma BDP AUC0-t

End point title	Plasma BDP AUC0-t

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*hr/mL				
arithmetic mean (standard deviation)	531.57 (± 170.6)	874.83 (± 384.71)	424.36 (± 181.78)	744.42 (± 455.82)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.17
upper limit	1.48

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.05
upper limit	1.56

Secondary: Plasma BDP AUC0-0.5h

End point title	Plasma BDP AUC0-0.5h

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*hr/mL				
arithmetic mean (standard deviation)	408.53 (± 118.48)	545.52 (± 191.73)	290.53 (± 123.94)	409.41 (± 232.19)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.49
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.33
upper limit	1.66

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.26
upper limit	1.67

Secondary: Plasma BDP AUC0-inf

End point title	Plasma BDP AUC0-inf

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*hr/mL				
arithmetic mean (standard deviation)	597.4 (± 162.19)	827.18 (± 304.72)	503.6 (± 180.95)	807.75 (± 469.8)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.07
upper limit	1.32

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.93
upper limit	1.25

Secondary: Plasma BDP Cmax

End point title	Plasma BDP Cmax

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg/mL				
arithmetic mean (standard deviation)	1546.3 (± 506.4)	2042.5 (± 877.7)	918.9 (± 396.4)	1243.6 (± 706.9)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.77

Confidence interval	
level	90 %
sides	2-sided
lower limit	1.55
upper limit	2.02

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.51
upper limit	2.03

Secondary: Plasma BDP tmax

End point title	Plasma BDP tmax

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hours				
median (full range (min-max))	0.1 (0.1 to 0.3)	0.1 (0.1 to 0.3)	0.1 (0.1 to 0.3)	0.1 (0.1 to 0.3)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.063
Method	Wilcoxon signed rank test

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.999
Method	Wilcoxon signed rank test

Secondary: Plasma BDP t1/2

End point title	Plasma BDP t1/2

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hours				
arithmetic mean (standard deviation)	0.29 (± 0.07)	0.36 (± 0.11)	0.39 (± 0.15)	0.43 (± 0.16)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.74
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.65
upper limit	0.83

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.82
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.71
upper limit	0.95

Secondary: Plasma formoterol AUC0-t

End point title	Plasma formoterol AUC0-t

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*hr/mL				
arithmetic mean (standard deviation)	93.44 (± 17.9)	115.05 (± 28.96)	67.8 (± 17.33)	78.9 (± 22.15)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.31
upper limit	1.49

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.46
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.36
upper limit	1.56

Secondary: Plasma formoterol AUC0-0.5h

End point title	Plasma formoterol AUC0-0.5h

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*hr/mL				
arithmetic mean (standard deviation)	18.45 (± 4.11)	24.93 (± 7.48)	8 (± 2.6)	10.73 (± 3.74)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	2.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.17
upper limit	2.66

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	2.37

Confidence interval	
level	90 %
sides	2-sided
lower limit	2.16
upper limit	2.6

Secondary: Plasma formoterol AUC0-∞

End point title	Plasma formoterol AUC0-∞
End point description:	
End point type	Secondary
End point timeframe:	
At Visit 2 and Visit 3	

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*h/mL				
arithmetic mean (standard deviation)	129.02 (± 24.73)	151.62 (± 43.96)	89.71 (± 24.46)	102.13 (± 34.58)

Statistical analyses

Statistical analysis title	CHF 1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.34
upper limit	1.57

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent

Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.36
upper limit	1.62

Secondary: Plasma formoterol Cmax

End point title	Plasma formoterol Cmax

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK.

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg/mL				
arithmetic mean (standard deviation)	57.79 (± 16.888)	87.39 (± 31.69)	21.535 (± 6.835)	31.83 (± 12.42)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	2.71

Confidence interval	
level	90 %
sides	2-sided
lower limit	2.45
upper limit	3

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	2.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	2.56
upper limit	3.13

Secondary: Plasma formoterol Tmax

End point title	Plasma formoterol Tmax

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hr				
median (full range (min-max))	0.1 (0.1 to 0.3)	0.1 (0.1 to 0.3)	0.25 (0.1 to 1)	0.1 (0.1 to 1)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0
Method	Wilcoxon signed rank test

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD v CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.145
Method	wilcoxon signed rank test

Secondary: Plasma formoterol T½

End point title	Plasma formoterol T½

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hr				
arithmetic mean (standard deviation)	4.87 (± 1.69)	4.25 (± 0.84)	4.18 (± 1.87)	3.7 (± 0.91)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults

Statistical analysis description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK

population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK

Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.04
upper limit	1.33

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.16
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.05
upper limit	1.28

Secondary: Plasma B17MP AUC0-0.05h

End point title	Plasma B17MP AUC0-0.05h

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*hr/mL				
arithmetic mean (standard deviation)	185.02 (± 64.03)	356.61 (± 110.13)	126.26 (± 47)	245.68 (± 139.7)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.34
upper limit	1.68

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Statistical analysis description:	
For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK	
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.59
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.37
upper limit	1.84

Secondary: Plasma B17MP AUC0-∞

End point title	Plasma B17MP AUC0-∞

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg*hr/mL				
arithmetic mean (standard deviation)	3065.42 (± 826.52)	3937.07 (± 792.82)	2809.98 (± 773.24)	3710.1 (± 1605.52)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.03
upper limit	1.17

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.98
upper limit	1.25

Secondary: Plasma B17MP Cmax

End point title	Plasma B17MP Cmax

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK

End point type	Secondary

End point timeframe:

at Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: pg/mL				
arithmetic mean (standard deviation)	612 (± 186.5)	1000.4 (± 246.5)	481.2 (± 113.7)	830.9 (± 355.5)

Statistical analyses

Statistical analysis title	ChF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.26

Confidence interval	
level	90 %
sides	2-sided
lower limit	1.16
upper limit	1.36

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.13
upper limit	1.37

Secondary: Plasma B17MP Tmax

End point title	Plasma B17MP Tmax

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hr				
median (full range (min-max))	1 (0.3 to 2)	0.5 (0.1 to 2)	1 (0.3 to 2)	1 (0.3 to 2)

Statistical analyses

Statistical analysis title	ChF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.008
Method	wilcoxon signed rank test

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.005
Method	wilcoxon signed rank test

Secondary: Plasma B17MP t1/2

End point title	Plasma B17MP t1/2

End point description:

For the purpose of the secondary endpoints analysis, the results are reported based on the PK population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PK

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hr				
arithmetic mean (standard deviation)	3.45 (± 0.74)	2.94 (± 1.03)	3.88 (± 0.94)	3.02 (± 0.99)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.82
upper limit	0.99

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.88
upper limit	1.08

Secondary: Plasma potassium Cmin

End point title	Plasma potassium Cmin

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD

End point type	Secondary

End point timeframe:

At visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: mEq/L				

arithmetic mean (standard deviation)	3.717 (± 0.254)	3.795 (± 0.212)	3.72 (± 0.214)	3.902 (± 0.197)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Statistical analysis description:	
For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD	
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.998
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.977
upper limit	1.02

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Statistical analysis description:	
For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD	
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.971
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.948
upper limit	0.995

Secondary: Plasma potassium Tmin

End point title	Plasma potassium Tmin

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD

End point type	Secondary

End point timeframe:

at Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hours				
median (full range (min-max))	4 (0 to 6)	1.88 (0.5 to 7.8)	4 (0 to 8)	4 (1 to 7.8)

Statistical analyses

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.162
Method	wilcoxon signed rank test

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD v CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.008
Method	wilcoxon signed rank test

Secondary: Plasma potassium AUC0-t

End point title	Plasma potassium AUC0-t

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol

deviation that could affect the PD

End point type	Secondary
End point timeframe: At Visit 2 and Visit 3	

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: mEq*h/L				
arithmetic mean (standard deviation)	31.81 (± 1.94)	31.68 (± 1.45)	32.14 (± 1.79)	32.35 (± 1.32)

Statistical analyses

Statistical analysis title	ChF1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.01

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1

Secondary: Plasma glucose Cmax

End point title	Plasma glucose Cmax

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: mg/dL				
arithmetic mean (standard deviation)	128.6 (± 22.9)	160.1 (± 35.3)	126.3 (± 17.1)	148.4 (± 14.5)

Statistical analyses

Statistical analysis title	CHf1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.07

Statistical analysis title	CHf1535 NEXT DPI vs BDP DPI + FF DPI in adolescen
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.15

Secondary: Plasma glucose Tmax

End point title	Plasma glucose Tmax

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hours				
median (full range (min-max))	4.02 (4 to 6.1)	4 (3.9 to 8)	4.02 (4 to 8)	4 (3.9 to 6)

Statistical analyses

Statistical analysis title	Chf1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.487
Method	wilcoxon signed rank test

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.216
Method	wilcoxon signed rank test

Secondary: Plasma glucose AUC0-2h

End point title	Plasma glucose AUC0-2h

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: mg*hr/dL				
arithmetic mean (standard deviation)	180.99 (± 11.55)	187.83 (± 16.9)	178.5 (± 10.78)	183.95 (± 12.81)

Statistical analyses

Statistical analysis title	Chf1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.03

Statistical analysis title	CHf1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.05

Secondary: Plasma glucose AUC0-t	
End point title	Plasma glucose AUC0-t
End point description:	
For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD	
End point type	Secondary
End point timeframe:	
At Visit 2 and Visit 3	

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: mg*hr/dL				
arithmetic mean (standard deviation)	848.52 (± 84.71)	956.7 (± 128.81)	829.42 (± 61.48)	910.22 (± 72.76)

Statistical analyses

Statistical analysis title	CHF 1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.05

Statistical analysis title	CHf1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.1

Secondary: Plasma cortisol Cmin

End point title	Plasma cortisol Cmin

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD

End point type	Secondary

End point timeframe:

at Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: ng/mL				
arithmetic mean (standard deviation)	38.98 (±	15.01 (±	40.98 (±	13.58 (± 8.06)

28.87)	13.93)	31.09)

Statistical analyses

Statistical analysis title	CHF 1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.16

Statistical analysis title	CHf1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.2

Secondary: Plasma cortisol Tmin

End point title	Plasma cortisol Tmin

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: hours				
median (full range (min-max))	4.02 (2 to 8.2)	6 (2 to 8)	4.02 (2 to 8.1)	4.03 (2 to 7.9)

Statistical analyses

Statistical analysis title	CHF 1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.695
Method	Wilcoxon signed rank testc

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.768
Method	Wilcoxon signed rank testc

Secondary: Plasma cortisol AUC0-t

End point title	Plasma cortisol AUC0-t

End point description:

For the purpose of the secondary pharmacodynamic endpoints analysis, the results are reported based on the PD population, namely the subpopulation of the safety population without any major protocol deviation that could affect the PD

End point type	Secondary

End point timeframe:

At Visit 2 and Visit 3

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: ng*hr/mL				
arithmetic mean (standard deviation)	571.93 (± 377.99)	257.09 (± 148.51)	596.53 (± 356.59)	264.86 (± 112.11)

Statistical analyses

Statistical analysis title	CHF 1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.07

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.06

Secondary: Peak FEV1

End point title	Peak FEV1

End point description:	
Pulmonary function values are calculated on the base of the safety population	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3. Lung Function (FEV1, FVC) was evaluated during each treatment period (Visit 2 and 3) at the scheduled time pre- and post-drug administration.	

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: Liters				
arithmetic mean (standard deviation)	3.799 (± 0.928)	3.049 (± 0.676)	3.819 (± 0.908)	3.15 (± 0.71)

Statistical analyses

Statistical analysis title	CHF 1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	least square mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.052
upper limit	0.013

Statistical analysis title	CHf1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	least square mean difference
Point estimate	-0.099

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.227
upper limit	0.029

Secondary: FEV1 AUC0-8h/8h

End point title	FEV1 AUC0-8h/8h

End point description:

Pulmonary function values are calculated on the base of the safety population

End point type	Secondary

End point timeframe:

At Visits 2 and 3. Lung Function (FEV1, FVC) was evaluated during each treatment period (Visit 2 and 3) at the scheduled time pre- and post-drug administration.

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: Liters				
arithmetic mean (standard deviation)	3.687 (± 0.904)	2.906 (± 0.64)	3.712 (± 0.904)	2.932 (± 0.644)

Statistical analyses

Statistical analysis title	CHF 1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.993
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.984
upper limit	1.001

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	0.993
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.964
upper limit	1.023

Secondary: Time average heart rate AUC0-8h/8h

End point title	Time average heart rate AUC0-8h/8h
End point description:	
Time average heart rate (AUC0-8h/8h) values are calculated on the base of the safety population	
End point type	Secondary
End point timeframe:	
At Visits 2 and 3. Heart rate was evaluated during each treatment period at the scheduled pre- ad post-drug administration	

End point values	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD	BDP DPI + FF DPI treatment phase - Adults - PK/PD	BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	27	30	27
Units: bpm				
arithmetic mean (standard deviation)	74 (± 9)	80.77 (± 8.72)	73 (± 9)	77.19 (± 9.61)

Statistical analyses

Statistical analysis title	CHF 1535 NEXT DPI vs BDP DPI + FF DPI in adults
Comparison groups	CHF 1535 100/6 NEXT DPI treatment phase - Adults - PK/PD v BDP DPI + FF DPI treatment phase - Adults - PK/PD
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.03

Statistical analysis title	CHF1535 NEXT DPI vs BDP DPI + FF DPI in adolescent
Comparison groups	CHF 1535NEXT DPI treatment phase - Adolescents - PK/PD v BDP DPI + FF DPI treatment phase - Adolescents - PK/PD
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANOVA
Parameter estimate	ratio of geometric means
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.09

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the overall duration of the study

Adverse event reporting additional description:

All analyses were performed on the Safety Population.
The number and percentage of patients experiencing AEs, study treatment-related AEs, SAEs and treatment-emergent AEs (TEAEs) leading to study discontinuation and severe AEs was presented for each treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	CHF1535 NEXT DPI - Adults - Safety
Reporting group description: -	
Reporting group title	CHF1535 NEXT DPI - Adolescents - Safety
Reporting group description: -	
Reporting group title	BDP DPI + FF DPI - Adults - Safety
Reporting group description: -	
Reporting group title	BDP DPI + FF DPI - Adolescents - Safety

Reporting group description: -

Serious adverse events	CHF1535 NEXT DPI - Adults - Safety	CHF1535 NEXT DPI - Adolescents - Safety	BDP DPI + FF DPI - Adults - Safety
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 28 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	BDP DPI + FF DPI - Adolescents - Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	CHF1535 NEXT DPI - Adults - Safety	CHF1535 NEXT DPI - Adolescents - Safety	BDP DPI + FF DPI - Adults - Safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 30 (40.00%)	1 / 28 (3.57%)	9 / 30 (30.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 30 (23.33%)	0 / 28 (0.00%)	5 / 30 (16.67%)
occurrences (all)	7	0	5
Tremor			
subjects affected / exposed	2 / 30 (6.67%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Syncope			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Mouth ulceration			
subjects affected / exposed	0 / 30 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
Oral herpes			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Tonsillitis			

subjects affected / exposed	0 / 30 (0.00%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	BDP DPI + FF DPI - Adolescents - Safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 27 (7.41%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Mouth ulceration			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Oral herpes			

subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2010	The total volume of blood that was withdrawn for the entire study was increased from 75 mL (adolescents) to 145 mL for patients in the adult population with the following changes to the volume of blood collected for the following PK and PD parameters for the adult population: - Formoterol: 9 blood samples of 3 mL. - BDP/B17MP: 9 blood samples of 2 mL. - Potassium: 9 blood samples of 1 mL. - Glucose: 9 blood samples of 1.2 mL. - Cortisol: 9 blood samples of 1 mL.

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.

No limitations and caveats are reported in the study document.

Notes: