Clinical trial results:
Control of moderate or severe asthma with 160, 320 and 640 mcg ciclesonide/day. A one-year randomised, double-blind, multicenter trial.

Summary

EudraCT number	2011-000683-99
Trial protocol	DE
Global end of trial date	15 August 2014

Results information

Result version number	v1
This version publication date	10 May 2016
First version publication date	10 May 2016

Trial information

Trial identification

Sponsor protocol code	CL-9709-301-RD

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1133-6333

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	61 Aldwych, London, United Kingdom, WC2B 4AE
Public contact	Program Manager, Takeda Development Centre Europe Ltd., +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Program Manager, Takeda Development Centre Europe Ltd., +1 877-825-3327, clinicaltrialregistry@tpna.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2014
Global end of trial reached?	Yes
Global end of trial date	15 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the trial is to investigate asthma control with 160 to 640 mcg ciclesonide/day. Asthma control will be assessed by the Asthma Control Questionnaire (ACQ).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2011
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	Argentina: 72
Country: Number of subjects enrolled	Brazil: 86
Country: Number of subjects enrolled	Germany: 60
Country: Number of subjects enrolled	Israel: 59
Country: Number of subjects enrolled	Russian Federation: 90
Worldwide total number of subjects	367
EEA total number of subjects	60

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)	16
Adults (18-64 years)	314
From 65 to 84 years	37

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 5 investigative sites in Argentina, Brazil, Germany, Israel and Russia from 10 November 2011 to 15 August 2014.

Pre-assignment

Screening details:

Subjects with a historical diagnosis of persistent bronchial asthma for at least 6 months,treated with a stable inhaled corticosteroid (ICS)dose for at least 12 weeks were enrolled in a single-blind baseline period receiving 160 microgram(mcg)ciclesonide,then a double-blind treatment period in 1 of 3 treatment arms: ciclesonide 160,320,640 mcg.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Period: Ciclesonide 160 mcg

Arm description:

Ciclesonide 80 mcg, metered dose inhaler (MDI), inhalational, twice daily for up to 3 weeks in the baseline period. Ciclesonide 80 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.

Arm type	Experimental
Investigational medicinal product name	Ciclesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Ciclesonide 80 mcg, metered dose inhaler (MDI), inhalational, twice daily for up to 3 weeks in the baseline period. Ciclesonide 80 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.

Arm title	Treatment Period: Ciclesonide 320 mcg

Arm description:

Ciclesonide 160 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.

Arm type	Experimental
Investigational medicinal product name	Ciclesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Ciclesonide 160 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.

Arm title	Treatment Period: Ciclesonide 640 mcg

Arm description:

Ciclesonide 320 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment

period.

Arm type	Experimental
Investigational medicinal product name	Ciclesonide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Ciclesonide 320 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.

Number of subjects in period 1	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg
Started	120	122	125
Completed	89	92	97
Not completed	31	30	28
Consent withdrawn by subject	16	12	9
Adverse event, non-fatal	1	1	3
Pregnancy	1	1	-
Miscellaneous	5	1	4
Discontinuation criterion fulfilled	2	-	2
Lost to follow-up	-	1	1
Deterioration in asthma	6	14	9

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period: Ciclesonide 160 mcg
Reporting group description:	
Ciclesonide 80 mcg, metered dose inhaler (MDI), inhalational, twice daily for up to 3 weeks in the baseline period. Ciclesonide 80 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.	
Reporting group title	Treatment Period: Ciclesonide 320 mcg
Reporting group description:	
Ciclesonide 160 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.	
Reporting group title	Treatment Period: Ciclesonide 640 mcg
Reporting group description:	
Ciclesonide 320 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.	

Reporting group values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg
Number of subjects	120	122	125
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	43.2	44.7	45.3
standard deviation	± 14.86	± 15.6	± 16.22
Gender, Male/Female			
Units: subjects			
Female	72	77	81
Male	48	45	44
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	6	5	4
White	113	115	114
Unknown or Not Reported	1	2	7
History of exacerbations			
Asthma exacerbations were defined as a worsening of asthma requiring either treatment with oral (or other systemic) glucocorticosteroids for at least 3 days or hospitalisation or a visit to the emergency room because of asthma.			
Units: Subjects			
0x	70	70	63
1x	17	19	21
2-3	4	3	4
4+	0	0	0
Unknown	29	30	37
Smoking Status			
Units: Subjects			
Never	109	102	109
Current	1	1	1
Former	10	19	15

Prestudy ICS dose Units: Subjects			
<200(mcg/day) fluticasone propionate(FP)equivalent	3	3	2
Low: ≥200 mcg/day (≤) 250 mcg/day FP equivalent	40	37	42
Medium:>250 mcg/day to ≤500 mcg/day FP equivalent	72	75	70
High:>500 mcg/day to ≤1000 mcg/day FP equivalent	5	7	11
Height Units: meter (m)			
arithmetic mean	1.65	1.66	1.65
standard deviation	± 0.093	± 0.101	± 0.104
Weight Units: kilograms (kg)			
arithmetic mean	74.59	77.98	73.72
standard deviation	± 16.371	± 18.993	± 14.66
Body Mass Index Units: kilogram per meter square (kg/m2)			
arithmetic mean	27.34	28.42	27.12
standard deviation	± 5.217	± 6.346	± 5.373
Baseline asthma control questionnaire (ACQ)			
ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled). The baseline ACQ score was defined as the average of the available measurements of the last 2 weeks at site before starting treatment.			
Units: units on scale			
arithmetic mean	2.24	2.16	2.2
standard deviation	± 0.304	± 0.384	± 0.361
Pre-forced expiratory volume in 1 second (FEV1)			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: liter (L)			
arithmetic mean	2.2	2.35	2.23
standard deviation	± 0.792	± 0.798	± 0.801
Post-FEV1			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: Lx			
arithmetic mean	2.71	2.84	2.76
standard deviation	± 0.915	± 0.883	± 0.906
FEV1 reversibility			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: Lx			
arithmetic mean	25.5	23	26.5
standard deviation	± 17.02	± 17.1	± 20.78
Pre FEV1 predicted			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: Lx			
arithmetic mean	69.095	74.345	71.835

standard deviation	± 18.4683	± 16.7285	± 18.4365
Post FEV1 predicted			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: Lx			
arithmetic mean	84.893	90.168	88.505
standard deviation	± 19.3038	± 17.7365	± 17.7105

Reporting group values	Total		
Number of subjects	367		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: subjects			
Female	230		
Male	137		
Race/Ethnicity, Customized			
Units: Subjects			
Black or African American	15		
White	342		
Unknown or Not Reported	10		
History of exacerbations			
Asthma exacerbations were defined as a worsening of asthma requiring either treatment with oral (or other systemic) glucocorticosteroids for at least 3 days or hospitalisation or a visit to the emergency room because of asthma.			
Units: Subjects			
0x	203		
1x	57		
2-3	11		
4+	0		
Unknown	96		
Smoking Status			
Units: Subjects			
Never	320		
Current	3		
Former	44		
Prestudy ICS dose			
Units: Subjects			
<200(mcg/day) fluticasone propionate(FP)equivalent	8		
Low: ≥200 mcg/day (≤) 250 mcg/day FP equivalent	119		
Medium:>250 mcg/day to ≤500 mcg/day FP equivalent	217		
High:>500 mcg/day to ≤1000 mcg/day FP equivalent	23		

Height Units: meter (m) arithmetic mean standard deviation	- -		
Weight Units: kilograms (kg) arithmetic mean standard deviation	- -		
Body Mass Index Units: kilogram per meter square (kg/m2) arithmetic mean standard deviation	- -		
Baseline asthma control questionnaire (ACQ)			
ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled). The baseline ACQ score was defined as the average of the available measurements of the last 2 weeks at site before starting treatment.			
Units: units on scale arithmetic mean standard deviation	- -		
Pre-forced expiratory volume in 1 second (FEV1)			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: liter (L) arithmetic mean standard deviation	- -		
Post-FEV1			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: Lx arithmetic mean standard deviation	- -		
FEV1 reversibility			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: Lx arithmetic mean standard deviation	- -		
Pre FEV1 predicted			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: Lx arithmetic mean standard deviation	- -		
Post FEV1 predicted			
FEV1 is the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration.			
Units: Lx arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Treatment Period: Ciclesonide 160 mcg
Reporting group description:	
Ciclesonide 80 mcg, metered dose inhaler (MDI), inhalational, twice daily for up to 3 weeks in the baseline period. Ciclesonide 80 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.	
Reporting group title	Treatment Period: Ciclesonide 320 mcg
Reporting group description:	
Ciclesonide 160 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.	
Reporting group title	Treatment Period: Ciclesonide 640 mcg
Reporting group description:	
Ciclesonide 320 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.	
Subject analysis set title	Treatment Periods: Ciclesonide 640 mcg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Ciclesonide 320 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.	

Primary: Asthma Control Questionnaire (ACQ) Score at Baseline

End point title	Asthma Control Questionnaire (ACQ) Score at Baseline[1]
End point description:	
ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled).Baseline was defined as the average of the ACQ measurements of the last 2 weeks at site prior to first intake of double-blind study medication.	
End point type	Primary
End point timeframe:	
Baseline	

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: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	119	122	
Units: units on a scale				
arithmetic mean (standard error)	2.24 (± 0.031)	2.15 (± 0.035)	2.19 (± 0.032)	

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in ACQ Score to Tlast

End point title	Change from Baseline in ACQ Score to Tlast

End point description:

ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled). Tlast was defined as the last postrandomization ACQ measurement.

End point type	Primary

End point timeframe:

Week 52

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	119	122	
Units: units on a scale				
arithmetic mean (standard error)	-0.833 (± 0.1028)	-0.799 (± 0.1019)	-0.955 (± 0.0969)	

Statistical analyses

Statistical analysis title	Ciclesonide 160 mcg vs Ciclesonide 640 mcg

Statistical analysis description:

Least square (LS) mean difference were derived from an ANCOVA model with baseline ACQ and age as covariates, and treatment, centre pool, sex, and prestudy ICS dose as factors.

Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2988
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.353
upper limit	0.109
Variability estimate	Standard error of the mean
Dispersion value	0.1175

Statistical analysis title	Ciclesonide 160 mcg vs Ciclesonide 320 mcg

Statistical analysis description:

LS mean difference were derived from an ANCOVA model with baseline ACQ and age as covariates, and treatment, centre pool, sex, and prestudy ICS dose as factors.

Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7741
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.198
upper limit	0.266
Variability estimate	Standard error of the mean
Dispersion value	0.118

Statistical analysis title	Ciclesonide 320 mcg vs Ciclesonide 640 mcg

Statistical analysis description:

LS mean difference were derived from an ANCOVA model with baseline ACQ and age as covariates, and treatment, centre pool, sex, and prestudy ICS dose as factors.

Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1835
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.387
upper limit	0.074
Variability estimate	Standard error of the mean
Dispersion value	0.1172

Secondary: Time Course of ACQ

End point title	Time Course of ACQ

End point description:

ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled). Baseline was defined as the average of the ACQ measurements of the last 2 weeks at site prior to first intake of double-blind study medication. The time course of ACQ was presented using descriptive statistics by visit and treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 52 (Treatment period)

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	108	115	
Units: Weeks				
median (full range (min-max))	1.1 (0 to 4.4)	1 (0 to 3.9)	1 (0 to 4.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Well-Controlled Asthma Over the Course of the Study

End point title	Time to Well-Controlled Asthma Over the Course of the Study

End point description:

The number of weeks with well-controlled asthma was defined as the number of weeks that the subject had an ACQ score of 0.75 or lower over the course of the study. ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled). Baseline was defined as the average of the ACQ measurements of the last 2 weeks at site prior to first intake of double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline up to Week 52 (treatment period)

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	119	122	
Units: weeks				
number (not applicable)	1211	1514	1447	

Statistical analyses

Statistical analysis title	Ciclesonide 160 mcg vs Ciclesonide 640 mcg
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4175
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann point estimate
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	5

Statistical analysis title	Ciclesonide 160 mcg vs Ciclesonide 320 mcg
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8465
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hodges-Lehmann point estimate
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	4

Secondary: Number of Subjects With Well-controlled Asthma and ACQ Improvement at the End of the Study

End point title	Number of Subjects With Well-controlled Asthma and ACQ Improvement at the End of the Study

End point description:

Well-controlled asthma at the end of the study was defined as a subject with an ACQ score of 0.75 or lower. ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled).ACQ improvement was defined as a subject with ACQ improvement of at least 0.5 at the end of the study.

End point type	Secondary

End point timeframe:

Week 52

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	122	125	
Units: subjects				
number (not applicable)				
Well-controlled Asthma	38	45	51	
ACQ Improvement	87	81	85	

Statistical analyses

Statistical analysis title	Wellcontrolled Asthma Ciclesonide 160mcgvs320mcg
Statistical analysis description: Well-controlled Asthma	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4186
Method	Fisher exact

Statistical analysis title	Wellcontrolled Asthma Ciclesonide 160mcgvs640mcg
Statistical analysis description: Well-controlled Asthma	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.146
Method	Fisher exact

Statistical analysis title	Wellcontrolled Asthma Ciclesonide 320mcgvs640mcg
Statistical analysis description: Well-controlled Asthma	
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6017
Method	Fisher exact

Statistical analysis title	ACQ Improvement Ciclesonide 160 mcg vs 320 mcg
Statistical analysis description: ACQ Improvement	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3305
Method	Fisher exact

Statistical analysis title	ACQ Improvement Ciclesonide 160 mcg vs 640 mcg
Statistical analysis description: ACQ Improvement	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.486
Method	Fisher exact

Statistical analysis title	ACQ Improvement Ciclesonide 320 mcg vs 640 mcg
Statistical analysis description: ACQ Improvement	
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8922
Method	Fisher exact

Secondary: Number of Subjects Reporting Time to First Well-Controlled Asthma and ACQ Improvement

End point title	Number of Subjects Reporting Time to First Well-Controlled

	Asthma and ACQ Improvement

End point description:

Well-controlled asthma at the end of the study was defined as a subject with an ACQ score of 0.75 or lower. ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled). ACQ improvement was defined as a subject with ACQ improvement of at least 0.5 at the end of the study. The time to first measurement of well-controlled asthma from randomization and the time to the first ACQ improvement from randomization was analyzed separately using a log-rank test. Baseline was defined as the average of the ACQ measurements of the last 2 weeks at site prior to first intake of double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline up to Week 52 (treatment period)

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	122	125	
Units: subjects				
number (not applicable)				
Well-controlled Asthma	73	84	81	
ACQ Improvement	112	107	115	

Statistical analyses

Statistical analysis title	Well-controlled Asthma Ciclesonide 160mcgvs640 mcg

Statistical analysis description:

Well-controlled Asthma

Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6062
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.221
Variability estimate	Standard error of the mean
Dispersion value	0.0806

Statistical analysis title	ACQ Improvement Ciclesonide 160 mcg vs 640 mcg
Statistical analysis description: ACQ Improvement	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4674
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.921
upper limit	1.197
Variability estimate	Standard error of the mean
Dispersion value	0.0669

Statistical analysis title	Well-controlled Asthma Ciclesonide 160mcgvs320 mcg
Statistical analysis description: Well-controlled Asthma	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2523
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.201
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.878
upper limit	1.642
Variability estimate	Standard error of the mean
Dispersion value	0.1597

Statistical analysis title	ACQ Improvement Ciclesonide 160 mcg vs 320 mcg
Statistical analysis description: ACQ Improvement	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg

Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5026
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.913
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.191
Variability estimate	Standard error of the mean
Dispersion value	0.1354

Statistical analysis title	Well-controlled Asthma Ciclesonide 320mcgvs640 mcg
Statistical analysis description:	
Well-controlled Asthma	
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4893
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.898
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.661
upper limit	1.219
Variability estimate	Standard error of the mean
Dispersion value	0.156

Statistical analysis title	ACQ Improvement Ciclesonide 320 mcg vs 640 mcg
Statistical analysis description:	
ACQ Improvement	
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2193
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.181

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.906
upper limit	1.538
Variability estimate	Standard error of the mean
Dispersion value	0.1351

Secondary: Number of Subjects Reporting Time to First Well-Controlled Asthma Measurement by ACQ Cut-Off Point

End point title	Number of Subjects Reporting Time to First Well-Controlled Asthma Measurement by ACQ Cut-Off Point

End point description:

Well-controlled asthma was defined as an ACQ score of equal to or lower than the ACQ cut-off point. ACQ score includes 5 questions about symptoms, beta-2 agonist use and lung function. Subjects recall their experiences during the previous 7 days and respond to each question using a 7-point scale ranging between 0 (well controlled) to 6 (extremely poorly controlled).The frequency of subjects below ACQ cut-off points of 0.5, 0.75, 1.0, 1.25, and 1.5 were analyzed over time using the site-based ACQ measurements. Baseline was defined as the average of the ACQ measurements of the last 2 weeks at site prior to first intake of double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline up to Week 52 (treatment period)

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	122	125	
Units: subjects				
number (not applicable)				
ACQ cut-off at 0.5	56	69	63	
ACQ cut-off at 1.0	91	95	93	
ACQ cut-off at 1.25	99	101	101	
ACQ cut-off at 1.5	103	105	107	

Statistical analyses

Statistical analysis title	ACQ cut-off at 0.5 Ciclesonide 160 mcg vs 640 mcg

Statistical analysis description:

ACQ cut-off at 0.5

Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5397
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.884
upper limit	1.266
Variability estimate	Standard error of the mean
Dispersion value	0.0917

Statistical analysis title	ACQ cut-off at 1.0 Ciclesonide 160 mcg vs 640 mcg
Statistical analysis description:	
ACQ cut-off at 1.0	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9458
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.161
Variability estimate	Standard error of the mean
Dispersion value	0.0738

Statistical analysis title	ACQ cut-off at 1.25 Ciclesonide 160 mcg vs 640 mcg
Statistical analysis description:	
ACQ cut-off at 1.25	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7213
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.026

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.893
upper limit	1.178
Variability estimate	Standard error of the mean
Dispersion value	0.0708

Statistical analysis title	ACQ cut-off at 1.5 Ciclesonide 160 mcg vs 640 mcg
Statistical analysis description: ACQ cut-off at 1.5	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4807
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.917
upper limit	1.202
Variability estimate	Standard error of the mean
Dispersion value	0.0692

Statistical analysis title	ACQ cut-off at 0.5 Ciclesonide 160 mcg vs 320 mcg
Statistical analysis description: ACQ cut-off at 0.5	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.115
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.326
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.934
upper limit	1.884
Variability estimate	Standard error of the mean
Dispersion value	0.1791

Statistical analysis title	ACQ cut-off at 1.0 Ciclesonide 160 mcg vs 320 mcg
Statistical analysis description: ACQ cut-off at 1.0	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6281
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.805
upper limit	1.431
Variability estimate	Standard error of the mean
Dispersion value	0.1467

Statistical analysis title	ACQ cut-off at 1.25 Ciclesonide 160 mcg vs 320 mcg
Statistical analysis description: ACQ cut-off at 1.25	
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6853
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.803
upper limit	1.397
Variability estimate	Standard error of the mean
Dispersion value	0.1415

Statistical analysis title	ACQ cut-off at 1.5 Ciclesonide 160 mcg vs 320 mcg
Statistical analysis description: ACQ cut-off at 1.5	

Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6995
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.804
upper limit	1.385
Variability estimate	Standard error of the mean
Dispersion value	0.1388

Statistical analysis title	ACQ cut-off at 0.5 Ciclesonide 320 mcg vs 640 mcg
Statistical analysis description:	
ACQ cut-off at 0.5	
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.308
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.837
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.595
upper limit	1.178
Variability estimate	Standard error of the mean
Dispersion value	0.1744

Statistical analysis title	ACQ cut-off at 1.0 Ciclesonide 160 mcg vs 640 mcg
Statistical analysis description:	
ACQ cut-off at 1.0	
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6645
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.939
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.705
upper limit	1.25
Variability estimate	Standard error of the mean
Dispersion value	0.1461

Statistical analysis title	ACQ cut-off at 1.25 Ciclesonide 160 mcg vs 640 mcg
Statistical analysis description:	
ACQ cut-off at 1.25	
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9564
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.992
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.753
upper limit	1.308
Variability estimate	Standard error of the mean
Dispersion value	0.1408

Statistical analysis title	ACQ cut-off at 1.5 Ciclesonide 160 mcg vs 640 mcg
Statistical analysis description:	
ACQ cut-off at 1.5	
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7367
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.047

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.371
Variability estimate	Standard error of the mean
Dispersion value	0.1375

Secondary: Number of Subjects Reporting Time to First Asthma Exacerbation

End point title	Number of Subjects Reporting Time to First Asthma Exacerbation

End point description:

Asthma exacerbations were defined as a worsening of asthma requiring either treatment with oral (or other systemic) glucocorticosteroids for at least 3 days or hospitalisation or a visit to the emergency room because of asthma. Baseline was defined as the average of the ACQ measurements of the last 2 weeks at site prior to first intake of double-blind study medication

End point type	Secondary

End point timeframe:

Baseline up to Week 52 (treatment period)

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	122	125	
Units: subjects				
number (not applicable)	5	11	10	

Statistical analyses

Statistical analysis title	Ciclesonide 160 mcg vs Ciclesonide 640 mcg
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2264
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.367
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.824
upper limit	2.267

Variability estimate	Standard error of the mean
Dispersion value	0.2583

Statistical analysis title	Ciclesonide 320 mcg vs Ciclesonide 640 mcg
Comparison groups	Treatment Period: Ciclesonide 320 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7732
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.375
upper limit	2.074
Variability estimate	Standard error of the mean
Dispersion value	0.4365

Statistical analysis title	Ciclesonide 160 mcg vs Ciclesonide 320 mcg
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1373
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.789
upper limit	5.602
Variability estimate	Standard error of the mean
Dispersion value	0.5001

Secondary: Number of Subjects Reporting Asthma Exacerbations Rates

End point title	Number of Subjects Reporting Asthma Exacerbations Rates

End point description:

These analyses intended to identify subject subsets that would benefit from dose escalation. This exploratory analysis tested the potential factors, including age, sex, pretrial ICS dose category, history of exacerbations, baseline ACQ score, baseline BMI category, and smoking status. Of these, age and

history of exacerbations were both found to be potential prognostic factors with relevant influence on ACQ. As predefined in the protocol, the results subjects with missing data for any category were not included. Baseline was defined as the average of the ACQ measurements of the last 2 weeks at site prior to first intake of double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline up to Week 52 (treatment period)

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Period: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	122	122	
Units: subjects				
number (not applicable)	5	10	10	

Statistical analyses

Statistical analysis title	Ciclesonide 160 mcg vs Ciclesonide 320 mcg
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 640 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.288
Method	Fisher exact

Statistical analysis title	Ciclesonide 160 mcg vs Ciclesonide 640 mcg
Comparison groups	Treatment Period: Ciclesonide 160 mcg v Treatment Period: Ciclesonide 320 mcg
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2864
Method	Fisher exact

Secondary: Number of Subjects With Markedly High Benefits.

End point title	Number of Subjects With Markedly High Benefits.[2]

End point description:

These analyses intended to identify subject subsets that would benefit from dose escalation. This exploratory analysis tested the potential factors, including age, sex, pretrial ICS dose category, history of exacerbations, baseline ACQ score, baseline BMI category, and smoking status. Of these, age and history of exacerbations were both found to be potential prognostic factors with relevant influence on ACQ. As predefined in the protocol, the results subjects with missing data for any category were not

included.

End point type	Secondary

End point timeframe:

Week 1 up to Week 52

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Ciclesonide 640 mcg arm has been reported as subject analysis set created additionally for this endpoint in order to report the 1 participant who was erroneously randomized into this treatment arm.

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Periods: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119	122	126	
Units: subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting One or More Treatment-emergent Adverse Events (TEAE)

End point title	Number of Subjects Reporting One or More Treatment-emergent Adverse Events (TEAE)[3]

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. TEAE is defined as an adverse event with an onset that occurs after receiving study drug. AEs included both serious AEs and non-serious AEs. Baseline of double-blind treatment period was defined as the average of the measurements of the last 2 weeks at site prior to first intake of double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline period (Week -3 up to -1), treatment period (Baseline up to Week 56)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Ciclesonide 640 mcg arm has been reported as subject analysis set created additionally for this endpoint in order to report the 1 participant who was erroneously randomized into this treatment arm.

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Periods: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119	122	126	
Units: subjects				
number (not applicable)	85	86	89	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Clinically Significant Change from Baseline in Vital Signs

End point title	Number of Subjects Reporting Clinically Significant Change from Baseline in Vital Signs[4]

End point description:

Vital signs included body temperature, blood pressure (BP) and pulse rate. Normal range for vital signs included: Systolic BP >170 millimeters of mercury (mm Hg) or <85 mm Hg, Diastolic BP >105 mm Hg, resting pulse rate: >120 bpm or <50 bpm, difference in systolic BP at Visit x (increase or decrease) compared with pretreatment >40 mm Hg and difference in pulse rate at Visit x (increase or decrease) compared with pretreatment >30 bpm. Baseline of double-blind treatment period was defined as the average of the measurements of the last 2 weeks at site prior to first intake of double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline period (Week -3 up to -1), treatment period (Baseline up to Week 56)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Ciclesonide 640 mcg arm has been reported as subject analysis set created additionally for this endpoint in order to report the 1 participant who was erroneously randomized into this treatment arm.

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Periods: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119	122	126	
Units: subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Clinically Significant Change from Baseline in Physical Examination Findings

End point title	Number of Subjects Reporting Clinically Significant Change from Baseline in Physical Examination Findings[5]

End point description:

Physical examination consists of examinations of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) physical examinations other than body systems described in (1) to (10). Baseline of double-blind

treatment period was defined as the average of the measurements of the last 2 weeks at site prior to first intake of double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline period (Week -3 up to -1), treatment period (Baseline up to Week 56)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Ciclesonide 640 mcg arm has been reported as subject analysis set created additionally for this endpoint in order to report the 1 participant who was erroneously randomized into this treatment arm.

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Periods: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119	122	126	
Units: subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Markedly Abnormal Laboratory Values

End point title	Number of Subjects With Markedly Abnormal Laboratory

End point description:

The number of subjects with any markedly abnormal standard safety laboratory values collected throughout study. Baseline of double-blind treatment period was defined as the average of the measurements of the last 2 weeks at site prior to first intake of double-blind study medication.

End point type	Secondary

End point timeframe:

Baseline period (Week -3 up to -1), treatment period (Baseline up to Week 56)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data for Ciclesonide 640 mcg arm has been reported as subject analysis set created additionally for this endpoint in order to report the 1 participant who was erroneously randomized into this treatment arm.

End point values	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 320 mcg	Treatment Periods: Ciclesonide 640 mcg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119	122	126	
Units: subjects				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are adverse events that started after the first dose of double-blind study drug and no more than 30 days for a serious adverse event after the last dose of double-blind study drug.

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the subject or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Treatment Period: Ciclesonide 160 mcg

Reporting group description:

Ciclesonide 80 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.

Reporting group title	Treatment Period: Ciclesonide 640 mcg

Reporting group description:

Ciclesonide 320 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.

Reporting group title	Treatment Period: Ciclesonide 320 mcg

Reporting group description:

Ciclesonide 160 mcg, MDI, inhalational, twice daily for up to 52 weeks in the double blind treatment period.

Serious adverse events	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 640 mcg	Treatment Period: Ciclesonide 320 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 119 (5.04%)	0 / 126 (0.00%)	9 / 122 (7.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			

subjects affected / exposed	1 / 119 (0.84%)	0 / 126 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 119 (0.84%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar ischaemia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 126 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autonomic nervous system imbalance			
subjects affected / exposed	1 / 119 (0.84%)	0 / 126 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 119 (0.84%)	0 / 126 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Invertebral disc protrusion			
subjects affected / exposed	1 / 119 (0.84%)	0 / 126 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	2 / 122 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			

subjects affected / exposed	0 / 119 (0.00%)	0 / 126 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment Period: Ciclesonide 160 mcg	Treatment Period: Ciclesonide 640 mcg	Treatment Period: Ciclesonide 320 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 119 (54.62%)	70 / 126 (55.56%)	65 / 122 (53.28%)
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 119 (18.49%)	16 / 126 (12.70%)	23 / 122 (18.85%)
occurrences (all)	67	58	82
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 119 (3.36%)	4 / 126 (3.17%)	7 / 122 (5.74%)
occurrences (all)	5	5	9
Rhinitis allergic			
subjects affected / exposed	8 / 119 (6.72%)	6 / 126 (4.76%)	3 / 122 (2.46%)
occurrences (all)	10	8	4
Cough			
subjects affected / exposed	6 / 119 (5.04%)	3 / 126 (2.38%)	7 / 122 (5.74%)
occurrences (all)	6	3	15
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 119 (3.36%)	8 / 126 (6.35%)	2 / 122 (1.64%)
occurrences (all)	7	14	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	18 / 119 (15.13%)	16 / 126 (12.70%)	16 / 122 (13.11%)
occurrences (all)	22	18	21
Influenza			
subjects affected / exposed	6 / 119 (5.04%)	11 / 126 (8.73%)	6 / 122 (4.92%)
occurrences (all)	6	12	7
Nasopharyngitis			

subjects affected / exposed	23 / 119 (19.33%)	22 / 126 (17.46%)	25 / 122 (20.49%)
occurrences (all)	31	37	32
Pharyngitis			
subjects affected / exposed	4 / 119 (3.36%)	4 / 126 (3.17%)	8 / 122 (6.56%)
occurrences (all)	4	6	11
Upper respiratory tract infection			
subjects affected / exposed	7 / 119 (5.88%)	6 / 126 (4.76%)	1 / 122 (0.82%)
occurrences (all)	7	6	1
Rhinitis			
subjects affected / exposed	2 / 119 (1.68%)	4 / 126 (3.17%)	8 / 122 (6.56%)
occurrences (all)	6	4	13
Sinusitis			
subjects affected / exposed	7 / 119 (5.88%)	8 / 126 (6.35%)	5 / 122 (4.10%)
occurrences (all)	7	10	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Refer ClinicalTrials.gov (CL-9709-301-RD,NCT01455194)results of Ciclesonide 160mcg arm baseline period because EUDRACT system does not allow the reporting of data available for the arm, which includes subjects that were not part of target population.

Notes: