Clinical trial results:
A single centre, open label, randomised, crossover study in dexamethasone-suppressed healthy adult male volunteers to compare the pharmacokinetics of Infacort® versus immediate-release hydrocortisone tablets at a single dose of 10mg and to evaluate the dose proportionality of Infacort® at doses of 0.5mg, 2mg, 5mg and 10mg.

Summary

EudraCT number	2013-000260-28
Trial protocol	GB
Global end of trial date	09 September 2013

Results information

Result version number	v1 (current)
This version publication date	13 June 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	Infacort 001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Diurnal Limited
Sponsor organisation address	Cardiff Medicentre, Cardiff, United Kingdom, CF14 4UJ
Public contact	info@diurnal.co.uk, Diurnal Limited, info@diurnal.co.uk
Scientific contact	info@diurnal.co.uk, Diurnal Limited, info@diurnal.co.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001283-PIP01-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2013
Global end of trial reached?	Yes
Global end of trial date	09 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objectives

•To compare the pharmacokinetics of Infacort® versus immediate-release hydrocortisone in a single dose of 10mg.

•To determine the dose proportionality for Infacort® at doses of 0.5mg, 2mg, 5mg and 10mg.

Protection of trial subjects:

The study protocol (Version 1, 17 April 2013), volunteer consent form (Version 2, 8 May 2013) and subject information sheet (Version 2, 8 May 2013) were approved by the South East Wales Research Ethics Committees (REC) on 13 May 2013.
Prior to undergoing any study-specific procedure, each potential study subject provided signed acknowledgement of their freely given informed consent. Either the Chief Investigator or a designated person, qualified to meet any applicable local regulations, who was equally knowledgeable about the study explained the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may have entailed. A corresponding written explanation (subject information sheet) was also provided and the subject allowed sufficient time to consider the study information.
Prior to signing the consent form, the subject was given an opportunity to discuss any issues concerning the study with a physician who had suitable knowledge of the study and had all questions answered openly and honestly.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2013
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment
Recruitment details: -

Pre-assignment
Screening details: -

Pre-assignment period milestones	
Number of subjects started	16
Number of subjects completed	16

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

Arms	
Are arms mutually exclusive?	No
Arm title	Infacort 0.5 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Infacort 0.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Each subject received 0.5 mg Infacort granules from 1 x 0.5 mg capsule of IMP on the morning of Day 2 at ~ 07.00 hrs (fasted). The Infacort® capsules were opened, the entire contents (multi-particulate granules) emptied onto a dosing spoon, administered to the back of the subject's tongue and swallowed with 200 mL water (100 mL to swallow the treatment and 100 mL rinse).

Each subject also received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22.00 hrs on Day 1, and at approximately 06.00 hrs and 12.00 hrs on Day 2.

Arm title	Infacort 2 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Infacort 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Each subject received 2 mg Infacort granules from 1 x 2 mg capsule of IMP on the morning of Day 2 at ~ 07.00 hrs (fasted). The Infacort® capsules were opened, the entire contents (multi-particulate granules) emptied onto a dosing spoon, administered to the back of the subject's tongue and swallowed with 200 mL water (100 mL to swallow the treatment and 100 mL rinse).

Each subject also received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22.00 hrs on Day 1, and at approximately 06.00 hrs and 12.00 hrs on Day 2.

Arm title	Infacort 5 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Infacort 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Each subject received 5 mg of Infacort granules from 1 x 5 mg capsule on the morning of Day 2 at ~ 07.00 hrs (fasted). The Infacort® capsules were opened, the entire contents (multi-particulate granules) emptied onto a dosing spoon, administered to the back of the subject's tongue and swallowed with 200 mL water (100 mL to swallow the treatment and 100 mL rinse).

Each subject also received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22.00 hrs on Day 1, and at approximately 06.00 hrs and 12.00 hrs on Day 2.

Arm title	Infacort 10 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Infacort 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Each subject received 10 mg of Infacort granules from 2 x 5 mg capsules on the morning of Day 2 at ~ 07.00 hrs (fasted). The Infacort® capsules were opened, the entire contents (multi-particulate granules) emptied onto a dosing spoon, administered to the back of the subject's tongue and swallowed with 200 mL water (100 mL to swallow the treatment and 100 mL rinse).

Each subject also received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22.00 hrs on Day 1, and at approximately 06.00 hrs and 12.00 hrs on Day 2.

Arm title	Hydrocortisone
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each subject received 1 x 10 mg hydrocortisone tablet on the morning of Day 2 at ~07.00 hrs (fasted). The hydrocortisone tablets were swallowed whole with 200 mL water.

Each subject also received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22.00 hrs on Day 1, and at approximately 06.00 hrs and 12.00 hrs on Day 2.

Number of subjects in period 1	Infacort 0.5 mg	Infacort 2 mg	Infacort 5 mg
Started	16	16	16
Completed	16	16	16

Number of subjects in period 1	Infacort 10 mg	Hydrocortisone
Started	16	16
Completed	16	16

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	16	16	
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	0	
Adults (18-64 years)	16	16	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	40.7		
standard deviation	± 14.37	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	16	16	

End points

End points reporting groups

Reporting group title	Infacort 0.5 mg
Reporting group description: -	
Reporting group title	Infacort 2 mg
Reporting group description: -	
Reporting group title	Infacort 5 mg
Reporting group description: -	
Reporting group title	Infacort 10 mg
Reporting group description: -	
Reporting group title	Hydrocortisone
Reporting group description: -	

Primary: Bioequivalence: Cmax

End point title	Bioequivalence: Cmax[1]

End point description:

Unadjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression.

End point type	Primary

End point timeframe:

PK blood samples for measurement of serum cortisol levels were collected on Day 2 pre-dose (-1 hr and – 0.5 hr) and 0 hr (07.00 hrs), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11 and 12 hr post-dose

Notes:

[1] - 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: Statistics are only presented for Infacort 10 mg and hydrocortisone tablets, in line with the primary end point.

End point values	Infacort 10 mg	Hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[2]	16		
Units: nmol/L				
geometric mean (standard deviation)	604.467 (± 139.6942)	622.384 (± 99.3543)		

Notes:

[2] - Subjects with inadequate cortisol suppression have been excluded.

Statistical analyses

Statistical analysis title	Infacort 10 mg vs Hydrocortisone 10 mg: Cmax

Statistical analysis description:

To compare PK between treatments, the logarithms of these PK parameters were analysed using a mixed effects analysis of variance (ANOVA) including fixed effects for sequence, period and treatment and a random effect for subject nested within sequence. Based on the analyses, point estimates and 90% CI for the treatment ratios were calculated by re-transformation of the logarithmic results given by the ANOVA.

Comparison groups	Hydrocortisone v Infacort 10 mg

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Geometric least square mean
Point estimate	94.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	83.51
upper limit	107.4

Notes:

[3] - Bioequivalence.
N.B. The EudraCT form automatically sums the number of subjects in both treatment groups, which is incorrect as this is a cross-over design. The correct number of subjects in this analysis is 14.
Statistical Analysis has been performed on baseline adjusted data.

Primary: Bioequivalence: AUC0-t

End point title	Bioequivalence: AUC0-t[4]

End point description:

Unadjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression.

End point type	Primary

End point timeframe:

PK blood samples for measurement of serum cortisol levels were collected on Day 2 pre-dose (-1 hr and – 0.5 hr) and 0 hr (07.00 hrs), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11 and 12 hr post-dose

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: Statistics are only presented for Infacort 10 mg and hydrocortisone tablets, in line with the primary end point.

End point values	Infacort 10 mg	Hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[5]	16		
Units: hr*nmol/L				
geometric mean (standard deviation)	1785.306 (± 312.7802)	1803.278 (± 266.1113)		

Notes:

[5] - Subjects with inadequate cortisol suppression have been excluded.

Statistical analyses

Statistical analysis title	Infacort 10 mg vs Hydrocortisone 10 mg: AUC0-t

Statistical analysis description:

To compare PK between treatments, the logarothms of these PK parameters were analysed using a mixed effects analysis of variance (ANOVA) including fixed effects for sequence, period and treatment and a random effect for subject nested within sequence. Based on these analyses, point estimates and 90% CI for the treatment ratios were calculated by re-transformation of the logarithmic results given by the ANOVA.

Comparison groups	Infacort 10 mg v Hydrocortisone

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Geometric least square mean
Point estimate	101.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	95.78
upper limit	107.09

Notes:

[6] - Bioequivalence.
N.B. The EudraCT form automatically sums the number of subjects in both treatment groups, which is incorrect as this is a cross-over design. The correct number of subjects in this analysis is 14.
Statistical analysis has been performed on baseline adjusted data.

Primary: Bioequivalence: AUC0-inf

End point title	Bioequivalence: AUC0-inf[7]

End point description:

Unadjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression.

End point type	Primary

End point timeframe:

PK blood samples for measurement of serum cortisol levels were collected on Day 2 pre-dose (-1 hr and – 0.5 hr) and 0 hr (07.00 hrs), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11 and 12 hr post-dose

Notes:

[7] - 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: Statistics are only presented for Infacort 10 mg and hydrocortisone tablets, in line with the primary end point.

End point values	Infacort 10 mg	Hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[8]	16		
Units: hr*nmol/L				
geometric mean (standard deviation)	1881.745 (± 311.6197)	1898.311 (± 295.1258)		

Notes:

[8] - Subjects with inadequate cortisol suppression have been excluded.

Statistical analyses

Statistical analysis title	Infacort 10 mg vs Hydrocortisone 10 mg: AUC0-inf

Statistical analysis description:

To compare PK between treatments, the logarithms of these PK parameters were analysed using a mixed effects analysis of variance (ANOVA) including fixed effects for sequence, period and treatment and a random effect for subject nested within sequence. Based on the analyses, point estimates and 90% CI for the treatment ratios were calculated by re-transformation of the logarithmic results given by the ANOVA.

Comparison groups	Infacort 10 mg v Hydrocortisone

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Geometric least square mean
Point estimate	101.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	95.45
upper limit	106.94

Notes:

[9] - Bioequivalence.
N.B. The EudraCT form automatically sums the number of subjects in both treatment groups, which is incorrect as this is a cross-over design. The correct number of subjects in this analysis is 14.
Statistical analysis has been performed on baseline adjusted data.

Primary: Bioequivalence: tmax

End point title	Bioequivalence: tmax[10]

End point description:

Unadjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression.

End point type	Primary

End point timeframe:

PK blood samples for measurement of serum cortisol levels were collected on Day 2 pre-dose (-1 hr and – 0.5 hr) and 0 hr (07.00 hrs), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11 and 12 hr post-dose

Notes:

[10] - 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: Statistics are only presented for Infacort 10 mg and hydrocortisone tablets, in line with the primary end point.

End point values	Infacort 10 mg	Hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[11]	16		
Units: hr				
median (standard deviation)	0.75 (± 0.4127)	1 (± 0.4171)		

Notes:

[11] - Subjects with inadequate cortisol suppression have been excluded.

Statistical analyses

Statistical analysis title	Infacort 10 mg vs Hydrocortisone 10 mg: tmax

Statistical analysis description:

An assessment of tmax was performed by using the Wilcoxon matched pairs test. In addition, a 95% non-parametric CI was constructed for the median difference in tmax based on the method of Campbell and Gardner.

Comparison groups	Infacort 10 mg v Hydrocortisone

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.4772
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.25

Notes:

[12] - Bioequivalence.
N.B. The EudraCT form automatically sums the number of subjects in both treatment groups, which is incorrect as this is a cross-over design. The correct number of subjects in this analysis is 14.
Statistical analysis has been performed on baseline adjusted data.

Primary: Dose proportionality: Cmax

End point title	Dose proportionality: Cmax[13]

End point description:

Unadjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression.

End point type	Primary

End point timeframe:

PK blood samples for measurement of serum cortisol levels were collected on Day 2 pre-dose (-1 hr and – 0.5 hr) and 0 hr (07.00 hrs), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11 and 12 hr post-dose

Notes:

[13] - 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: Statistics are only presented for Infacort 0.5 mg, 2 mg, 5 mg and 10 mg, in line with the primary end point.

End point values	Infacort 0.5 mg	Infacort 2 mg	Infacort 5 mg	Infacort 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[14]	16	15[15]	14[16]
Units: nmol/L				
geometric mean (standard deviation)	90.092 (± 20.1404)	242.798 (± 39.4013)	418.313 (± 59.8826)	604.467 (± 139.6942)

Notes:

[14] - Subjects with inadequate cortisol suppression have been excluded.

[15] - Subjects with inadequate cortisol suppression have been excluded.

[16] - Subjects with inadequate cortisol suppression have been excluded.

Statistical analyses

Statistical analysis title	Dose proportionality - Slope: Cmax

Statistical analysis description:

Dose proportionality was assessed by performing a regression analysis of the log-transformed Cmax, AUC0-t and AUC0-inf values versus the log-transformed dose using the power model with a fixed effect for dose and a random effect for subject. For each parameter a point estimate and 95% CI has been calculated for the slope of the regression line.

Comparison groups	Infacort 0.5 mg v Infacort 2 mg v Infacort 5 mg v Infacort 10 mg

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[17]
Parameter estimate	Slope
Point estimate	0.702
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.658
upper limit	0.746

Notes:

[17] - Dose-proportionality.
N.B. The EudraCT form automatically sums the number of subjects in both treatment groups, which is incorrect as this is a cross-over design. The correct number of subjects in this analysis is 15.
Statistical analysis has been performed on baseline adjusted data.

Primary: Dose proportionality: AUC0-t

End point title	Dose proportionality: AUC0-t[18]

End point description:

Unadjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression.

End point type	Primary

End point timeframe:

PK blood samples for measurement of serum cortisol levels were collected on Day 2 pre-dose (-1 hr and – 0.5 hr) and 0 hr (07.00 hrs), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11 and 12 hr post-dose.

Notes:

[18] - 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: Statistics are only presented for Infacort 0.5 mg, 2 mg, 5 mg and 10 mg, in line with the primary end point.

End point values	Infacort 0.5 mg	Infacort 2 mg	Infacort 5 mg	Infacort 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[19]	16	15[20]	14[21]
Units: hr*nmol/L				
geometric mean (standard deviation)	316.973 (± 57.2979)	648.407 (± 108.8652)	1111.031 (± 163.7324)	1785.306 (± 312.7802)

Notes:

[19] - Subjects with inadequate cortisol suppression have been excluded.

[20] - Subjects with inadequate cortisol suppression have been excluded.

[21] - Subjects with inadequate cortisol suppression have been excluded.

Statistical analyses

Statistical analysis title	Dose proportionality - Slope: AUC0-t

Statistical analysis description:

Dose proportionality was assessed by performing a regression analysis of the log-transformed Cmax, AUC0-t and AUC0-inf values versus the log-transformed dose using the power model with a fixed effect for dose and a random effect for subject. For each parameter a point estimate and 95% CI has been calculated for the slope of the regression line.

Comparison groups	Infacort 0.5 mg v Infacort 2 mg v Infacort 5 mg v Infacort 10 mg

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[22]
Parameter estimate	Slope
Point estimate	0.858
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.833
upper limit	0.883

Notes:

[22] - Dose-proportionality.
N.B. The EudraCT form automatically sums the number of subjects in both treatment groups, which is incorrect as this is a cross-over design. The correct number of subjects in this analysis is 15.
Statistical Analysis has been performed on baseline adjusted data.

Primary: Dose proportionality: AUC0-inf

End point title	Dose proportionality: AUC0-inf[23]

End point description:

Unadjusted data excluding individual treatment profiles from subjects where the pre-dose cortisol demonstrated inadequate suppression.

End point type	Primary

End point timeframe:

PK blood samples for measurement of serum cortisol levels were collected on Day 2 pre-dose (-1 hr and – 0.5 hr) and 0 hr (07.00 hrs), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11 and 12 hr post-dose.

Notes:

[23] - 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: Statistics are only presented for Infacort 0.5 mg, 2 mg, 5 mg and 10 mg, in line with the primary end point.

End point values	Infacort 0.5 mg	Infacort 2 mg	Infacort 5 mg	Infacort 10 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[24]	16	15[25]	14[26]
Units: hr*nmol/L				
geometric mean (standard deviation)	505.706 (± 161.927)	790.269 (± 143.6361)	1213.237 (± 241.5286)	1881.745 (± 311.6197)

Notes:

[24] - Subjects with inadequate cortisol suppression have been excluded.

[25] - Subjects with inadequate cortisol suppression have been excluded.

[26] - Subjects with inadequate cortisol suppression have been excluded.

Statistical analyses

Statistical analysis title	Dose proportionality - Slope: AUC0-inf

Statistical analysis description:

Dose proportionality was assessed by performing a regression analysis of the log-transformed Cmax, AUC0-t and AUC0-inf values versus the log-transformed dose using the power model with a fixed effect for dose and a random effect for subject. For each parameter a point estimate and 95% CI has been calculated for the slope of the regression line.

Comparison groups	Infacort 0.5 mg v Infacort 2 mg v Infacort 5 mg v Infacort 10 mg

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[27]
Parameter estimate	Slope
Point estimate	0.855
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.829
upper limit	0.881

Notes:

[27] - Dose-proportionality.
N.B. The EudraCT form automatically sums the number of subjects in both treatment groups, which is incorrect as this is a cross-over design. The correct number of subjects in this analysis is 15.
Statistical analysis was performed using baseline adjusted data.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Only treatment-emergent AEs (TEAEs), i.e. existing conditions that worsened or events that occurred during the course of the study after administration of study drug, are included within the summary tables.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Infacort 0.5 mg
Reporting group description: -	
Reporting group title	Infacort 2 mg
Reporting group description: -	
Reporting group title	Infacort 5 mg
Reporting group description: -	
Reporting group title	Infacort 10 mg
Reporting group description: -	
Reporting group title	Hydrocortisone
Reporting group description: -	

Serious adverse events	Infacort 0.5 mg	Infacort 2 mg	Infacort 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Infacort 10 mg	Hydrocortisone	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Infacort 0.5 mg	Infacort 2 mg	Infacort 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	0 / 16 (0.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Infacort 10 mg	Hydrocortisone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)	1 / 16 (6.25%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Headache			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia oral			
subjects affected / exposed	2 / 16 (12.50%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported