Clinical trial results:
Open-label, long-term follow-up of safety and biochemical disease control of Infacort® in neonates, infants and children with congenital adrenal hyperplasia and adrenal insufficiency previously enrolled in the Infacort 003 study.

Summary

EudraCT number	2015-000458-40
Trial protocol	DE
Global end of trial date	10 August 2018

Results information

Result version number	v1 (current)
This version publication date	14 February 2019
First version publication date	14 February 2019

Trial information

Trial identification

Sponsor protocol code	Infacort 004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02733367
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Diurnal Limited
Sponsor organisation address	Cardiff Medicentre, Heath Park, Cardiff, United Kingdom, CF14 4UJ
Public contact	Dena Digweed, Diurnal Limited, +44 (0) 2920 682 069, info@diurnal.co.uk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 August 2018
Global end of trial reached?	Yes
Global end of trial date	10 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to gather data on the long-term safety of Infacort in subjects who completed study Infacort 003.

The secondary objective was to gather data on the effects of Infacort.

Protection of trial subjects:

Before enrolment, every subject (both parents/carers) received full oral and written information about the nature, purpose, expected advantages and possible risks of the study. The parents/carers agreed to participation in the study by signing the informed consent form. They were given an opportunity to enquire about details of the study. After a sufficient period of time (at least 24 hours) for the individual's consideration and decision, comprehension and consent were documented on the consent form by the dated signature of both the subject's parents/carers and the Investigator. Children aged 3 to 6 years were informed about their involvement in the study in the presence of their parents/carers.

Background therapy:

Not applicable for this study.

Evidence for comparator:

Not applicable for this study.

Actual start date of recruitment	04 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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	6

months)	
Children (2-11 years)	12
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects recruited were those who had satisfactorily completed study Infacort 003 and agreed to participate in study Infacort 004. The investigator ensured that all subjects who were treated in study Infacort 003 were invited to participate.

Pre-assignment

Screening details:

Subject selection was confirmed by checking through all protocol inclusion and exclusion criteria at the initial visit for this study.

Period 1

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

Blinding implementation details:

Not applicable for this study.

Arms

Arm title	Infacort

Arm description:

This was a non-randomised, open-label, single-group study; all subjects who participated received Infacort. One subject was initially withdrawn from the study, but subsequently re-enrolled.

Arm type	Experimental
Investigational medicinal product name	Infacort
Investigational medicinal product code	INF
Other name	Infacort is now authorised in the European Union as Alkindi (EU/1/17/1260)
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Infacort consists of immediate release granules, in dose strengths of 0.5mg, 1mg, 2mg and 5mg hydrocortisone, filled in a hard capsule; the capsule is a storage carrier and is not for consumption.

The granules were administered orally; either directly onto the top, and towards the back, of the child’s tongue; or indirectly onto the top and towards the back of the child’s tongue using a spoon; or the granules were sprinkled onto a spoonful of yoghurt, fruit purees (e.g. apple sauce) or fruit mousses immediately before being administered.

The granules could also be washed down with water, breast milk, formula milk or whole milk following administration.

Subjects received the usual clinically appropriate dose as determined by the Investigator, which was administered according to usual clinical practice – generally 3 or 4 times a day.

Number of subjects in period 1	Infacort
Started	18
Completed	12
Not completed	6
Consent withdrawn by subject	6

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	18	18	
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	6	6	
Children (2-11 years)	12	12	
Age continuous			
Mean subject age in days (safety population)			
Units: days			
arithmetic mean	1021.6		
standard deviation	± 650.84	-	
Gender categorical			
Subject gender (safety population)			
Units: Subjects			
Female	8	8	
Male	10	10	
Ethnic origin			
Ethnic origin of subjects			
Units: Subjects			
White (Caucasian)	18	18	
Body mass index			
Body mass index (kg/square meter)			
Units: kilogram(s)/square meter			
arithmetic mean	17.02		
standard deviation	± 2.083	-	
Body surface area			
Body surface area (square meter)			
Units: square meter			
arithmetic mean	0.582		
standard deviation	± 0.1803	-	

End points

End points reporting groups

Reporting group title	Infacort

Reporting group description:

This was a non-randomised, open-label, single-group study; all subjects who participated received Infacort. One subject was initially withdrawn from the study, but subsequently re-enrolled.

Primary: Nature and occurrence of adverse events

End point title	Nature and occurrence of adverse events[1]

End point description:

The primary endpoint was the nature and occurrence of serious adverse events (SAEs) and adverse events (AEs) observed throughout the study. AEs were recorded from the time of the first intake of Infacort until the final visit.

End point type	Primary

End point timeframe:

Assessed throughout the duration of the study.

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: The primary endpoint was the nature and occurrence of SAEs and AEs observed throughout the study; thus only descriptive statistical methods were used in the analyses of the data.

End point values	Infacort			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Number of events				
Treatment-emergent adverse events (TEAEs)	193			
Mild TEAEs	151			
Moderate TEAEs	42			
Severe TEAEs	0			
Serious TEAEs	9			
TEAEs leading to withdrawal	0			
TEAEs related to Infacort	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Growth Velocity SDS

End point title	Growth Velocity SDS

End point description:

Body height/length (cm) was obtained at each visit by specially trained paediatric endocrine nurses or physicians using standard calibrated auxological methods.

End point type	Other pre-specified

End point timeframe:

Growth velocity standard deviation score (SDS) at visit 6 (11th month) and visit 10 (23rd month).

End point values	Infacort			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Standard Deviation Score				
arithmetic mean (standard deviation)				
Visit 6 - 11th Month (n=10)	0.6343 (± 2.51996)			
Visit 10 - 23rd Month (n=9)	0.9214 (± 1.88757)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cortisol levels - blood spot analysis

End point title	Cortisol levels - blood spot analysis

End point description:

The dried blood spots were analysed for multi-steroids, including cortisol (all subjects). Blood spot absolute laboratory values for the safety population are presented.

End point type	Other pre-specified

End point timeframe:

A dried blood spot sample was collected at the initial and final visits, every month for the first 2 months of the study and thereafter every 6 months.

End point values	Infacort			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: nanomole(s)/litre				
arithmetic mean (standard deviation)				
Visit 1 (n=14)	43.329 (± 48.3217)			
Final Visit (n=12)	22.022 (± 27.1323)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time of the first intake of Infacort in this study until the final study visit.

Adverse event reporting additional description:

Details of any adverse events were collected, including date of onset, end date, frequency, severity, seriousness, relationship to Infacort, action taken, and outcome. Any adverse event was followed, whenever possible, until it returned to the baseline condition or became stable with no further change expected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Infacort (safety population)

Reporting group description:

Safety population (all subjects who received one complete or partial dose of Infacort).

Serious adverse events	Infacort (safety population)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Infacort (safety population)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 18 (77.78%)		
Investigations			
Body temperature increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Tooth injury			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Venomous sting			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Injury			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Scar			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Vascular disorders			
Secondary hypertension			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Surgical and medical procedures			
Genitourinary operation			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Circumcision			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 18 (55.56%)		
occurrences (all)	45		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	7		
Abdominal pain upper			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Dental caries			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	12		
Reproductive system and breast disorders			
Vulval disorder			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pharyngeal erythema			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Dermatitis allergic			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Synovitis			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Scoliosis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	6		
Conjunctivitis			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	6		
Enterovirus infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	8 / 18 (44.44%)		
occurrences (all)	11		
Gastroenteritis viral			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Molluscum contagiosum			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Otitis media				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	2			
Otitis media viral				
subjects affected / exposed	3 / 18 (16.67%)			
occurrences (all)	3			
Pharyngitis				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	2			
Pharyngotonsillitis				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	2 / 18 (11.11%)			
occurrences (all)	2			
Roseola				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	3 / 18 (16.67%)			
occurrences (all)	3			
Viral infection				
subjects affected / exposed	6 / 18 (33.33%)			
occurrences (all)	6			
Viral upper respiratory tract infection				
subjects affected / exposed	7 / 18 (38.89%)			
occurrences (all)	21			
Scarlet fever				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			
Upper respiratory tract infection				
subjects affected / exposed	1 / 18 (5.56%)			
occurrences (all)	1			

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2016	Protocol amendment 1 - the following changes to the protocol were included in this amendment: Interim data analyses were expected to be required for regulatory review as part of any Marketing Authorisation Applications. As such a statement to this effect was added to the statistical methods section of the synopsis and in Section 13. In addition to the Infacort granules being administered directly onto the top, and towards the back, of the child's tongue, it was added that the granules could also be sprinkled onto yoghurt, fruit purees (e.g. apple sauce) or fruit mousses immediately before being administered to the child. The granules could also be washed down with water, breast milk, formula milk or whole milk following administration. This information was added to Section 10.2.1 of the protocol. In Section 8.5 (Previous and Concomitant Medication/Treatment) the protocol incorrectly stated that the trade names of the medications should be provided. This was amended to specify that generic names should be stated. The timing of the blood spot samples was clarified to state that these should be taken in the morning wherever possible, since this is usually the time of poor control. The statistical analysis section was updated to confirm that the change from baseline at each visit for continuous and categorical data would only be conducted if appropriate. Section 10.2.2 of the protocol (Packaging and Labelling) was updated to state that Infacort capsules would be supplied in either blister packs or bottles.

20 July 2017	Protocol amendment 2 - the following changes to the protocol were included in this amendment: It was confirmed that AEs, whether or not they are considered serious, leading to the application of sick day rules and use of sick day medication and which lead to any medical intervention either sought or required, such as at a hospital/clinic, are to be considered to be AEs of special interest. In addition, any occurrence of adrenal crisis must be recorded as an AE of special interest. In some cases, whilst the subject is cared for at the study site for the purposes of the study, it may be necessary for the Investigator to visit the subject at their local hospital. A detailed procedure for this scenario has been added as an appendix to the protocol. The wording around administration of the granules was amended to say that the granules can be sprinkled onto a spoonful of yoghurt, fruit purees (e.g. apple sauce) or fruit mousses rather than using the term 'mixed'. A footnote was added stating that at the time of submission of this amendment (protocol version 4.0), Infacort is the subject of an ongoing Marketing Authorisation Application procedure and that for clarity, the end of study visits for each subject will occur after Infacort is commercially available locally. It was added that if a visit needs to be postponed for more than 10 days, then the subject should attend for the visit before the period of absence for safety and drug supply reasons. Subsequent visits will then be scheduled at regular intervals from the revised early visit date. Testing of hydrocortisone acetate in the blood spot analyses was removed since this is no longer analysed. It was decided that the secondary endpoint of growth velocity would not be used, but instead the standard deviation score for height and weight would be calculated for each subject using an age- and gender-matched healthy German reference cohort. This change was implemented throughout the protocol.

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.

This study was designed as a safety study to evaluate the long-term use of Infacort in routine clinical practice. Efficacy results should be viewed as exploratory and interpreted with care.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30058902