



Clinical trial results:

A Phase 3 open-label study of Infacort® in neonates, infants and children less than 6 years of age with adrenal insufficiency.

Summary

EudraCT number	2014-002265-30
Trial protocol	DE
Global end of trial date	20 May 2016

Results information

Result version number	v1 (current)
This version publication date	22 December 2016
First version publication date	22 December 2016

Trial information

Trial identification

Sponsor protocol code	Infacort003
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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, Heath Park, Cardiff, United Kingdom, CF14 4UJ
Public contact	David English, Diurnal Limited, 44 2920682069, davidenglish@diurnal.co.uk
Scientific contact	David English, Diurnal Limited, 44 2920682069, davidenglish@diurnal.co.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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	05 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 May 2016
Global end of trial reached?	Yes
Global end of trial date	20 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate significant absorption of hydrocortisone from the Infacort® preparation.

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 trial. The parents/carers agreed to participation in the trial 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 1 night) 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/treating doctor. Children aged 3 to 6 years were informed about their involvement in the study in the presence of their parents/carers. Both the subject information and the subject consent forms were prepared in duplicate. One of each form was kept by the Investigator, and the other was given to the subject or their parents/carers.

All information sheets and consent forms were provided in German, the country in which the study was conducted.

Since only one dose of the subject's usual IRHC was replaced with Infacort® and the dose used was the same as the IRHC dose the subject was receiving before the study, the risk of study participation was considered to be minimal. Children usually take their medication every 8 hours so the maximum sampling period up to 8 hours after the Infacort® dose would not delay the subject's usual dosing pattern. Further risk minimisation was provided by treating older children (who are more robust and less prone to hypoglycaemia due to steroid deficiency) before the younger children, and proceeding to the younger children only after a satisfactory assessment of all safety data by the IDMC.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	6
Infants and toddlers (28 days-23 months)	6
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:

- 12 subjects aged ≥ 2 and < 6 years were studied in Cohort 1.
- 6 subjects ≥ 28 days and < 2 years were studied in Cohort 2.
- 6 subjects < 28 days were studied in the third cohort.

All subjects were recruited to a single centre site in Germany. Subjects could be recruited remotely, but needed to visit the site in order to participate.

Pre-assignment

Screening details:

A total of 24 subjects were studied in 3 cohorts (as agreed in the PIP):

- 12 subjects aged ≥ 2 and < 6 years were studied in Cohort 1.
- 6 subjects ≥ 28 days and < 2 years were studied in Cohort 2.
- 6 subjects < 28 days were studied in the third cohort.

Period 1

Period 1 title	Cohort 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Subjects aged 2 - < 6 years
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Arm description:

The study consisted of 3 consecutive parts. Cohort 1 included 12 subjects aged between 2 and < 6 years. No safety concerns emerged after review of this cohort, so 6 subjects aged 28 days to < 2 years were enrolled (Cohort 2). No safety concerns were raised after a review of accumulated data so 6 neonates aged from birth to < 28 days were enrolled (Cohort 3). The decision to continue after each cohort was based on the recommendation of the IDMC.

Arm type	Experimental
Investigational medicinal product name	Infacort
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Administration of Infacort® took place approximately 8 hours following the subject's prior hydrocortisone dose. The subject had to fast for at least 2 hours (45 minutes for children below 1 year of age) before the dose and were asked not to eat until after the sampling at 60 minutes (30 minutes below 1 year of age). Details of meals (e.g. time of eating and content of meal) were recorded in the CRF.

The Infacort® capsule was opened and the entire contents (i.e. drug granules) were administered either:

1. Directly onto the top, and towards the back of the child's tongue, by the study nurse/Investigator and washed down immediately with fluid (water, breast milk, formula milk, juice).
2. Indirectly onto the top, and towards the back of the child's tongue, by the study nurse/Investigator using a spoon and washed down immediately with fluid (water, breast milk, formula milk, juice).

The time, dose, and any other details were recorded in the CRF.

Number of subjects in period 1^[1]	Subjects aged 2 - <6 years
Started	12
Completed	12

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The study consisted of three consecutive cohorts. Cohort 1 included 12 subjects aged between 2 and < 6 years. As no safety concerns emerged, 6 subjects aged 28 days to <2 years were enrolled (Cohort 2). A review of accumulated data was then undertaken and again, no safety concerns emerged, so 6 neonates aged from birth to <28 days were enrolled (Cohort 3).

The decision to continue after each cohort was based on the recommendation of an Independent Data Monitoring Committee.

Period 2

Period 2 title	Cohort 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Arm title	Subjects aged 28 days to <2 years
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Infacort
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Administration of Infacort® took place approximately 8 hours following the subject's prior hydrocortisone dose. The subject had to fast for at least 2 hours (45 minutes for children below 1 year of age) before the dose and were asked not to eat until after the sampling at 60 minutes (30 minutes below 1 year of age). Details of meals (e.g. time of eating and content of meal) were recorded in the CRF.

The Infacort® capsule was opened and the entire contents (i.e. drug granules) were administered either:

1. Directly onto the top, and towards the back of the child's tongue, by the study nurse/Investigator and washed down immediately with fluid (water, breast milk, formula milk, juice).
2. Indirectly onto the top, and towards the back of the child's tongue, by the study nurse/Investigator using a spoon and washed down immediately with fluid (water, breast milk, formula milk, juice).

The time, dose, and any other details were recorded in the CRF.

Number of subjects in period 2 ^[2]	Subjects aged 28 days to <2 years
Started	6
Completed	6

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The study consisted of three consecutive cohorts. Cohort 1 included 12 subjects aged between 2 and < 6 years. As no safety concerns emerged, 6 subjects aged 28 days to <2 years were enrolled (Cohort 2). A review of accumulated data was then undertaken and again, no safety concerns emerged, so 6 neonates aged from birth to <28 days were enrolled (Cohort 3).

The decision to continue after each cohort was based on the recommendation of an Independent Data Monitoring Committee.

Period 3

Period 3 title	Cohort 3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Blinding implementation details:	
N/A	

Arms

Arm title	Subjects aged <28 days
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Infacort
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Administration of Infacort® took place approximately 8 hours following the subject's prior hydrocortisone dose. The subject had to fast for at least 2 hours (45 minutes for children below 1 year of age) before the dose and were asked not to eat until after the sampling at 60 minutes (30 minutes below 1 year of age). Details of meals (e.g. time of eating and content of meal) were recorded in the CRF.

The Infacort® capsule was opened and the entire contents (i.e. drug granules) were administered either:

1. Directly onto the top, and towards the back of the child's tongue, by the study nurse/Investigator and washed down immediately with fluid (water, breast milk, formula milk, juice).
2. Indirectly onto the top, and towards the back of the child's tongue, by the study nurse/Investigator using a spoon and washed down immediately with fluid (water, breast milk, formula milk, juice).

The time, dose, and any other details were recorded in the CRF.

Number of subjects in period 3	Subjects aged <28 days
Started	6
Completed	6

Baseline characteristics

Reporting groups

Reporting group title	Subjects aged 2 - <6 years
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Reporting group description:

The study consisted of 3 consecutive parts. Cohort 1 included 12 subjects aged between 2 and <6 years. No safety concerns emerged after review of this cohort, so 6 subjects aged 28 days to <2 years were enrolled (Cohort 2). No safety concerns were raised after a review of accumulated data so 6 neonates aged from birth to <28 days were enrolled (Cohort 3). The decision to continue after each cohort was based on the recommendation of the IDMC.

Reporting group values	Subjects aged 2 - <6 years	Total	
Number of subjects	12	12	
Age categorical			
Units: Subjects			
Children (2 to <6 years)	12	12	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	7	7	

End points

End points reporting groups

Reporting group title	Subjects aged 2 - <6 years
Reporting group description: The study consisted of 3 consecutive parts. Cohort 1 included 12 subjects aged between 2 and <6 years. No safety concerns emerged after review of this cohort, so 6 subjects aged 28 days to <2 years were enrolled (Cohort 2). No safety concerns were raised after a review of accumulated data so 6 neonates aged from birth to <28 days were enrolled (Cohort 3). The decision to continue after each cohort was based on the recommendation of the IDMC.	
Reporting group title	Subjects aged 28 days to <2 years
Reporting group description: -	
Reporting group title	Subjects aged <28 days
Reporting group description: -	

Primary: Maximum levels of serum cortisol concentration up to 240 minutes after intake of study drug as determined by the central laboratory.

End point title	Maximum levels of serum cortisol concentration up to 240 minutes after intake of study drug as determined by the central laboratory.
End point description: The objective of this endpoint is to demonstrate significant absorption of hydrocortisone from the Infacort preparation.	
End point type	Primary
End point timeframe: Up to 240 minutes post-administration with Infacort	

End point values	Subjects aged 2 - <6 years	Subjects aged 28 days to <2 years	Subjects aged <28 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	6	6	
Units: P-value				
number (not applicable)	0.0005	0.0313	0.0313	

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Statistical analysis description: At the maximum cortisol level (i.e. at C _{max}) a statistically significant increase was seen in cortisol levels compared to baseline for all cohorts combined (p<0.0001). Thus the primary endpoint of the study was met. A statistically significant difference compared to baseline was seen in Cohort 1 (p=0.0005), but for Cohorts 2 and 3, although all subjects showed an increase in cortisol, the difference from baseline was not statistically significant (p=0.0313 at the 1% level).	
Comparison groups	Subjects aged 28 days to <2 years v Subjects aged <28 days v Subjects aged 2 - <6 years

Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Sign test

Secondary: Serum cortisol concentration up to 6 hours after intake of study drug as determined by the central laboratory

End point title	Serum cortisol concentration up to 6 hours after intake of study drug as determined by the central laboratory
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End point description:

End point type	Secondary
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End point timeframe:

Up to 6 hours post-administration of Infacort

End point values	Subjects aged 2 - <6 years	Subjects aged 28 days to <2 years	Subjects aged <28 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	4	5	
Units: P-value				
number (not applicable)	0.00001	0.4654	0.0905	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from the time of first intake of Infacort® until Visit 4.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	All subjects
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Reporting group description:

All 24 subjects were included within the AE reporting group for the study (Also referred to as the "safety population")

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 24 (33.33%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Possetting (infantile spitting up)	Additional description: Considered to be a form of reflux rather than vomiting,		

subjects affected / exposed occurrences (all)	hence coding separately.		
	1 / 24 (4.17%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2		
Hyperhidrosis subjects affected / exposed occurrences (all)	Additional description: Excessive sweating		
	1 / 24 (4.17%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2015	<p>The protocol was amended to allow the following changes:</p> <ul style="list-style-type: none">• Collection of full date of birth. <p>Changes in important parameters that affect disposition of molecules such as hydrocortisone are age-related. These parameters most importantly include absorption, volume of distribution & clearance. As an example, paracetamol (acetaminophen) clearance (L/hr) increases from 2.02 L/hr at 1 month of age to 4.09 L/hr at 1 year of age and to 14.27 L/hr at 16 years of age (Krasniak et al., 2014). Therefore, collection of year of birth only in subjects is insufficient to enable accurate interpretation of results. Section 13 of the Parent Information Sheet has been amended accordingly.</p> <p>Originally, the protocol allowed for full date of birth in Section 8.4 but was inconsistent with respect to Section 15.8. The informed consent form however did not allow for collection of the full date of birth.</p> <ul style="list-style-type: none">• Change to the method of Investigational Medicinal Product (IMP) administration. <p>In Cohort 1 the Investigator administered the IMP in accordance with parent/carer preference and usual clinical practice. The amended protocol now reflects the actual methods of IMP administration adopted during Cohort 1.</p> <ul style="list-style-type: none">• Change to the storage temperature of serum blood samples. <p>The change to the storage temperature of serum blood samples is necessary to reflect freezer availability in the study site sample processing facility.</p> <ul style="list-style-type: none">• Provision for direct blood sampling if cannulation is not considered suitable by the Investigator. <p>In the younger subjects (Cohorts 2 & 3) it might not be appropriate to insert a cannula due to the small size of the subject's veins. In this event a small needle will be used for direct venous blood sampling. This will result in a maximum of 2 venous punctures at each timepoint.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None.

Notes: