

CLINICAL STUDY PROTOCOL PLUS AMENDMENT 2

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

Protocol No.: Infacort 004
EudraCT No.: 2015-000458-40
Version No.: Final 4.0
Date of Protocol: 20 July 2017

STUDY SPONSOR:

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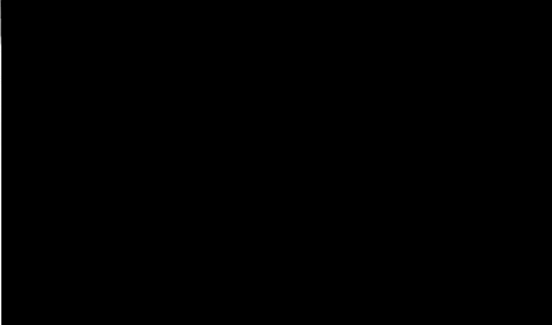

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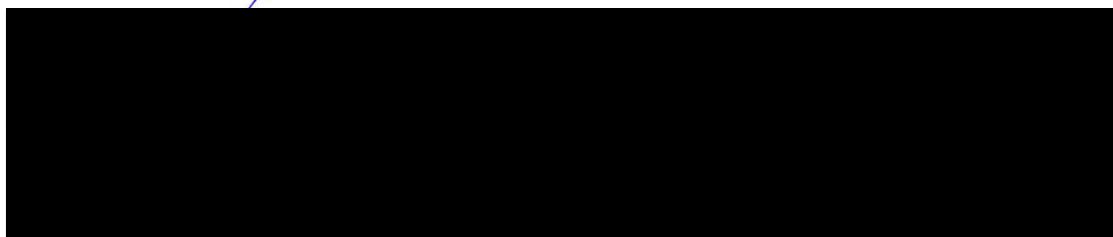
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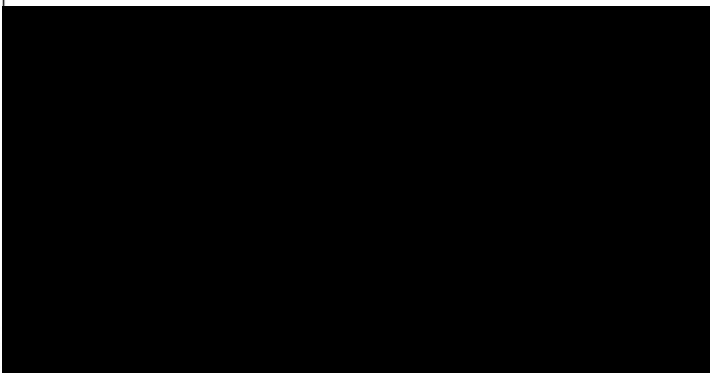
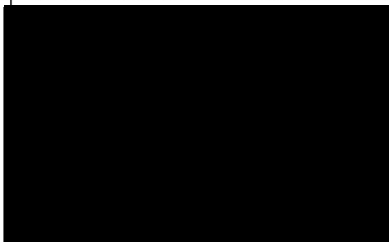
Principal Coordinating Investigator Address:	
Tel: Fax: Email:	

I, the undersigned, have reviewed this Protocol plus amendment 2, and including Appendices, and I will conduct the clinical study as described and will adhere to GCP/ICH and all the ethical and regulatory considerations stated. I have read and understood the contents of the Investigator's Brochure.

Signature:

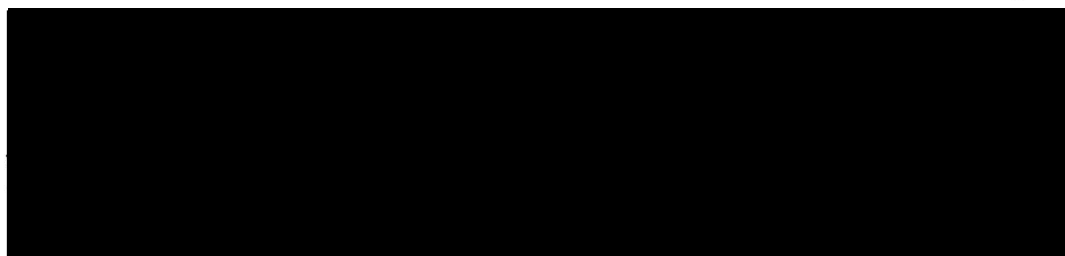


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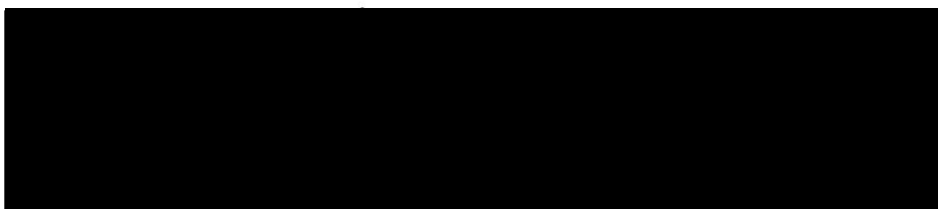


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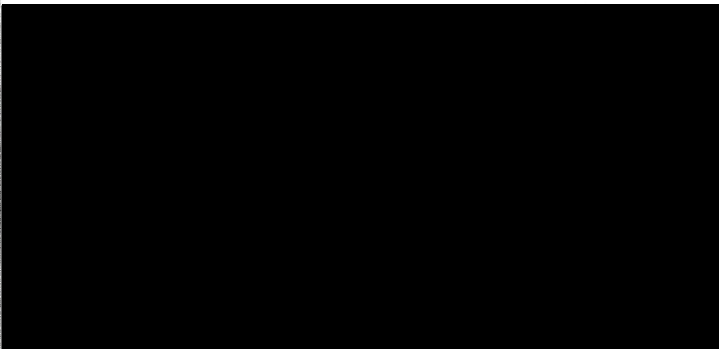

Sub-Investigator Address:	
Tel: Fax: Email:	

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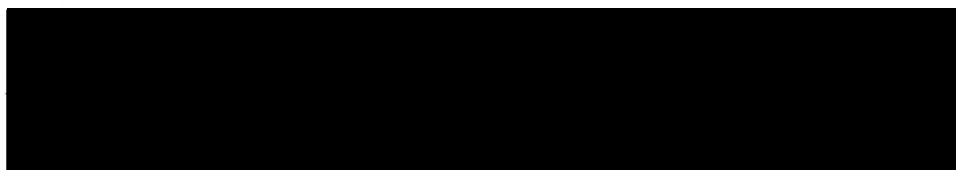


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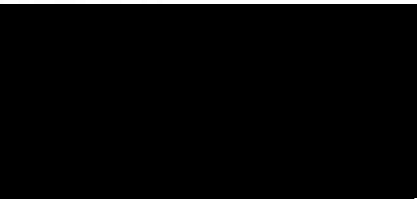
<p>Sub-Investigator</p> <p>Address:</p>	
<p>Tel:</p> <p>Fax:</p> <p>Email:</p>	

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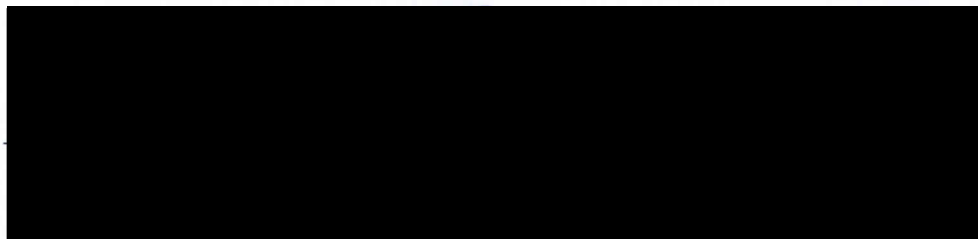


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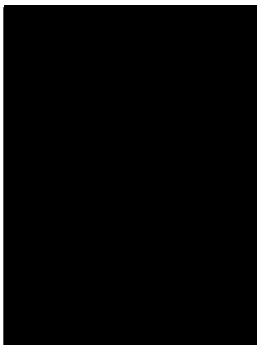
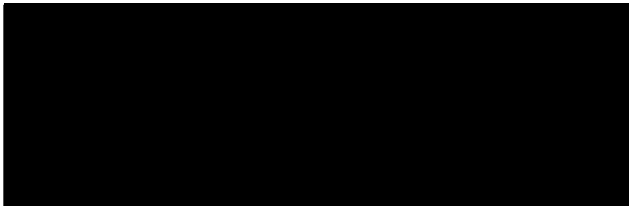
Statistician: Address:	
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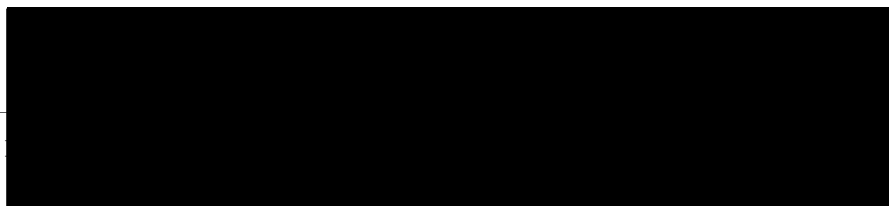


MEDICAL MONITOR SIGNATURE PAGE

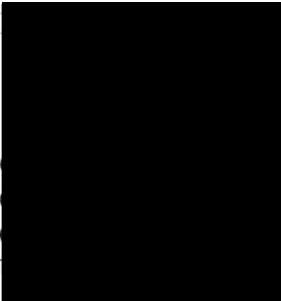

Medical Monitor: Address:	
Tel: Fax: Email:	

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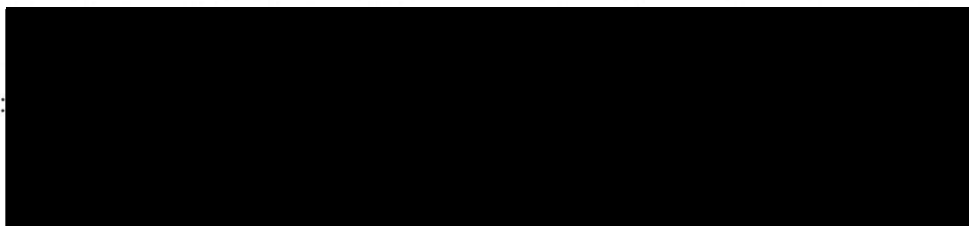


REPRESENTATIVE OF THE SPONSOR SIGNATURE PAGE

Representative of the Sponsor: Address:	
Tel: Fax: Email:	

I, the undersigned, have reviewed this Protocol plus amendment 2, and including Appendices, and I will conduct my role in the clinical study as described and will adhere to GCP/ICH and all the ethical and regulatory considerations stated. I have read and understood the contents of the Investigator's Brochure.

Signature:



1. Protocol Synopsis

PROTOCOL TITLE:	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	
PROTOCOL No:	Infacort 004	EudraCT No.: 2015-000458-40
PRINCIPAL INVESTIGATOR:	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	
DEPUTIES OF THE INVESTIGATOR AND SUB-INVESTIGATORS:	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	
SPONSOR:	<p>Diurnal Limited</p> <p>Cardiff Medicentre</p> <p>Heath Park</p> <p>Cardiff, CF14 4UJ</p> <p>United Kingdom</p>	
REPRESENTATIVE OF THE SPONSOR:	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	
INVESTIGATIONAL PRODUCT:	Infacort® granules	
PHASE OF DEVELOPMENT:	Phase 3	
INDICATION AND RATIONALE:	<p><i>Indication:</i> Treatment of adrenal insufficiency (AI) in children.</p> <p><i>Rationale:</i> This protocol is based on a Paediatric Investigation Plan (PIP) that has been agreed by the EMA (EMEA-001283-PIP01-12).</p> <p>AI in children is most commonly congenital, either primary due to congenital adrenal failure or secondary due to congenital hypopituitarism. All causes result in cortisol deficiency and the commonest cause of primary adrenal failure is congenital adrenal hyperplasia (CAH), usually caused by 21-hydroxylase deficiency, which results in cortisol deficiency and androgen excess, with or without aldosterone deficiency. Treatment for all causes of AI is with hydrocortisone administered 3 to 4 times daily. Current standard treatment in neonates is unsatisfactory, as unlicensed adult dosage formulations (hydrocortisone tablets, 10 mg) are used which are crushed and an approximate dose created prior to administration. There is thus no standard for</p>	

	<p>formulation, the dose administered is unpredictable, the preparations have a bitter taste and are difficult to administer. Crushing tablets and administration of doses of 0.5 to 5.0 mg in neonates and infants is therefore inaccurate. Recent analysis of prescribed hydrocortisone for infants and neonates undertaken in Germany showed that 30% of studied crushed tablet batches missed the acceptance criteria for precision of mass and/or content of the European Pharmacopeia (Kauzor et al., 2014).</p> <p>Infacort® is a newly developed paediatric and neonatal formulation of immediate release hydrocortisone that is provided in appropriate unit dosage (0.5 mg, 1.0 mg, 2.0 mg and 5 mg). It has good bioavailability and stability, taste masking and predictable pharmacokinetics. The Infacort® development program is underpinned by a detailed Phase 1 study in normal, healthy adult volunteers which demonstrated bioequivalence to licensed hydrocortisone 10 mg tablets and dose linearity from 0.5 to 10 mg.</p> <p>The present protocol is designed to allow subjects who have taken part in study Infacort 003 (EudraCT number 2014-002265-30) an opportunity to receive Infacort® on a continuing basis until a regulatory decision has been taken regarding a marketing authorisation.</p>
<p>STUDY DESIGN AND SUMMARY OF PROCEDURES:</p>	<p>This is a Phase 3, open-label, single-group, non-randomised, observational study of the safety and biochemical disease control of Infacort® in neonates, infants and children with AI who have completed study Infacort 003. All subjects who have satisfactorily completed study Infacort 003 will be offered the opportunity to take part in Infacort 004.</p> <p>Setting: Specialist endocrine centres which treat children with AI.</p> <p>The protocol for follow-up will include:</p> <ul style="list-style-type: none"> • An initial visit • Monthly visits for the first 2 months of treatment • Thereafter visits every 3 months • Final visit <p>The study will be conducted in up to 24 subjects from the Infacort 003 study requiring replacement therapy for AI due to either CAH, primary adrenal failure or hypopituitarism. The primary site will be Charité-Universitätsmedizin Berlin, CVK. However, some subjects participating in Infacort 003 were enrolled at remote sites. Should their parents/carers consent to participation in Infacort 004, additional study centres will be involved or, if agreeable, the subjects may be cared for at Charité Universitätsmedizin Berlin for the purposes of the study, either having their visits conducted at Charité-Universitätsmedizin Berlin or having the Investigator at Charité-Universitätsmedizin Berlin visiting the subject at their local hospital. Parents/carers will be provided with the informed consent document at least 24 hours prior to enrolment of their child in the study. Children aged over 3 years old will be informed about their involvement in the study in the presence of their parents/carers.</p> <p>At each visit the following measures will be collected:</p> <ul style="list-style-type: none"> • Height/length and weight • Heart rate

	<ul style="list-style-type: none"> • Blood pressure (if possible) • Metabolic parameters including cortisol (all subjects) and androgens (17-hydroxyprogesterone [17-OHP], androstenedione [A4] and testosterone) in CAH subjects only, from dried blood spot analysis (every month for the first 2 months of the study, then every 6 months unless required after 3 months) • Blood sampling for electrolytes, renin, haematocrit, and any additional cortisol data (where collected for routine care) • Dose of Infacort® (except at final visit) • Other drug treatment • Tanner development stage • Problems associated with dosing (e.g., choking) • Serious and non-serious adverse events (SAEs and AEs), including application of sick day rules and adrenal crises <p>For each visit, care will be taken to note the time of blood sampling, and the time and dose of the previous administration of glucocorticoid. Subjects will also receive all their standard treatments during the study.</p> <p>Initial Visit: Date of birth, gender, race/ethnicity, and medical history will be retrieved from Infacort 003 data. Other assessments at this visit include:</p> <ul style="list-style-type: none"> • Informed consent • Changes in medical history/current medical status since enrolment in the Infacort 003 study • Physical examination • Height/length • Weight • Body mass index (BMI) and body surface area (BSA) (derived) • Vital signs <ul style="list-style-type: none"> ○ Blood pressure (if possible) ○ Heart rate ○ Temperature • Compliance with inclusion/exclusion criteria • Previous and concomitant medications (including current adrenal replacement therapy) • Infacort® administration education for parents/carers • Infacort® administration by the parent/carer in the presence of the Investigator. • Problems associated with administration/dosing - entire or incomplete dosing will be recorded in the case report form (CRF) • Dried blood spot sampling (cortisol [all subjects], and 17-OHP, A4, testosterone [CAH subjects only]) • Blood sampling (electrolytes, renin, haematocrit and any additional cortisol data) if taken as part of routine clinical care • Tanner development stage
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	<p>Interim Visits:</p> <ul style="list-style-type: none"> • Physical examination • Height/length • Weight • BMI and BSA (derived) • Vital signs <ul style="list-style-type: none"> ○ Blood pressure (if possible) ○ Heart rate ○ Temperature • Concomitant medication • Dose of Infacort® • Problems associated with administration/dosing • SAEs and AEs, including application of sick day rules and adrenal crises • Dried blood spot sampling (cortisol [all subjects], and 17-OHP, A4, testosterone [CAH subjects only]) every month for the first 2 months of the study, then every 6 months, unless required after 3 months • Blood sampling (electrolytes, renin, haematocrit and any additional cortisol data) where taken as part of routine clinical care (normally once a year) • Tanner development stage <p>Final Visit:</p> <ul style="list-style-type: none"> • Physical examination • Height/length • Weight • BMI and BSA (derived) • Vital signs <ul style="list-style-type: none"> ○ Blood pressure (if possible) ○ Heart rate ○ Temperature • Concomitant medication • Problems associated with administration/dosing • SAEs and AEs, including application of sick day rules and adrenal crises • Dried blood spot sampling (cortisol [all subjects], and 17-OHP, A4, testosterone [CAH subjects only]) • Blood sampling (electrolytes, renin, haematocrit and any additional cortisol data) if taken as part of routine clinical care • Tanner development stage • End of study information
OBJECTIVES:	<p><u>Primary objective:</u></p> <ul style="list-style-type: none"> • To gather data on the long-term safety of Infacort® in subjects completing study Infacort 003 <p><u>Secondary objectives:</u></p> <ul style="list-style-type: none"> • To gather data on the effects of Infacort®
ENDPOINTS:	<p><u>Primary endpoint:</u></p> <ul style="list-style-type: none"> • Nature and occurrence of SAEs and AEs observed throughout the study

	<u>Secondary endpoints:</u> <ul style="list-style-type: none"> Standard deviation score (SDS) for height and weight Cortisol (all subjects) and adrenal androgen levels (17-OHP, A4, testosterone) in CAH subjects only
METHODOLOGY	
NUMBER OF SUBJECTS (PLANNED):	Maximum of 24 subjects
SUBJECTS:	Children who have successfully completed study Infacort 003
PRINCIPAL INCLUSION CRITERIA	<p>Subjects successfully completing study Infacort 003, whose inclusion criteria were:</p> <ol style="list-style-type: none"> Male and female children less than 6 years of age. A diagnosis of AI as confirmed by an inappropriately low cortisol usually with other supporting tests. Receiving appropriate adrenocortical replacement therapy (hydrocortisone with/without fludrocortisone). Adequately hydrated and nourished. <p>In addition, the parents/carers must be able to understand and give written Informed Consent (according to AMG §40 (1) 3b) for this extension study.</p>
PRINCIPAL EXCLUSION CRITERIA:	<ol style="list-style-type: none"> Clinically evident acute AI (adrenal crisis) (Note: the subject can be re-evaluated for eligibility once the episode is over) Inability of the child to take oral therapy Subjects with clinical signs of acute infection or fever on inclusion (Note: the subject can be re-evaluated for eligibility once the episode is over) Any surgical or medical condition that in the opinion of the Investigator may place the subject at higher risk from his/her participation in the study Parents/carers of subjects unwilling to consent to saving and propagation of pseudonymised medical data for study reasons Subjects who are in a dependent relationship with the Investigator or the Sponsor
WITHDRAWAL CRITERIA:	<p>Subjects may be withdrawn from the study for any reason and without prejudice to further treatment in the following instances:</p> <ol style="list-style-type: none"> Withdrawal of consent (by the parent/carer) New medical conditions that may compromise the safety of the subject Decision of the Investigator if he/she considers the subject's health may be compromised by remaining in the study <p>The study may be terminated at any time in the event of:</p> <ol style="list-style-type: none"> Emerging data from the study suggests an unfavourable risk-benefit analysis New scientific evidence provided during the study that could affect the subject's safety (benefit-risk analysis no longer positive) Request of the Sponsor, the Independent Data Monitoring Committee (IDMC) or regulatory agency

INVESTIGATIONAL PRODUCT	
FORMULATION//DOSE:	Infacort® is a dry granule formulation of hydrocortisone stored in capsules that will be available in different strengths (0.5, 1.0, 2.0 and 5.0 mg). The clinically-appropriate dose, based on standard individualised treatment, will be administered according to usual clinical practice – usually 3 or 4 times daily.
ROUTE OF ADMINISTRATION:	Oral
DURATION AND FREQUENCY:	According to usual clinical practice
REFERENCE THERAPY	
FORMULATION//DOSE:	None
CRITERIA FOR EVALUATION	
BIOCHEMICAL DISEASE CONTROL ASSESSMENTS	SDS score for height and weight, cortisol (all subjects), and 17-OHP, A4 and testosterone (CAH subjects only)
SAFETY ASSESSMENTS:	SAEs, AEs, vital signs, and laboratory assessments
STATISTICAL METHODS:	No formal sample size calculation is provided for this study since only subjects who have previously been treated in study Infacort 003 can enter this study. Only descriptive statistical methods will be used for the evaluation of this study. All recorded and derived variables will be presented for each age cohort and overall using standard procedures (depending on the underlying distribution: for continuous data, sample size, mean, standard deviation (SD), minimum, median and maximum; for categorical data, sample size, absolute and relative frequency). The behaviour over time of continuous and categorical data will be analysed by presenting summary statistics for the actual values and change from baseline at each visit, if appropriate. Graphical presentations of the concentration data over time will also be provided. All collected and derived data will be listed. Interim data analyses are expected to be required for regulatory review as part of any marketing authorisation applications.
DATA MONITORING COMMITTEE:	Safety data will be reviewed by an IDMC on a regular basis to identify any emerging safety issues. An analysis of safety and biochemical disease control will be undertaken on a yearly basis, which will be overseen by the IDMC (this may be abbreviated in the early years when there is insufficient data to undertake a full analysis).
ESTIMATED DATE OF FIRST SUBJECT ENROLLED:	August 2015
ESTIMATED DATE OF LAST SUBJECT COMPLETED:	Subjects can continue to be treated in this study until they meet the study withdrawal criteria, Infacort® is granted a marketing authorisation (and so is available commercially ¹), Infacort® is

¹ At the time of submission of this amendment (protocol version 4.0), Infacort® is the subject of an ongoing Marketing Authorisation Application procedure. For clarity, the end of study visits for each subject will occur after Infacort is commercially available.

	refused a marketing authorisation, or the Sponsor decides to discontinue the study.
NUMBER OF STUDY CENTRES:	The main centre and remote sites participating in Infacort 003

2. List of Abbreviations

17-OHP	17-hydroxyprogesterone
A4	Androstenedione
AE	Adverse event
ACTH	Adrenocorticotrophic hormone
ADR	Adverse drug reaction
AI	Adrenal insufficiency
AUC	Area under the plasma concentration versus time curve
AUC _{0-t}	AUC from the time of dosing to the time of the last observed concentration
AUC _{0-inf}	AUC extrapolated to infinity from dosing time, based on the last observed concentration
BMI	Body mass index
BSA	Body surface area
CAH	Congenital adrenal hyperplasia
CI	Confidence interval
C _{max}	Maximum plasma concentration
CRF	Case report form
CRH	Corticotropin-releasing hormone
CSR	Clinical study report
CV	Coefficient of variation
EU	European Union
GCP	Good Clinical Practice
HDPE	High-density polyethylene
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Millilitre
NF	National Formulary
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PP	Polypropylene
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDS	Standard deviation score
SDV	Source data verification
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction

$t_{1/2}$	Half-life
T_{max}	Time at which C_{max} occurs
UPI	Unique product identifier
WHO	World Health Organisation
μg	Microgram
μL	Microlitre

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4. Investigators and Administrative Structure

Principal Investigator

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
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[REDACTED]

Medical Monitor (Sponsor)

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[REDACTED]
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Laboratory for Blood Spot Analysis

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5. Introduction

5.1 Background on the Disease

Adrenal insufficiency (AI) may be classified as primary (dysfunction of the adrenal gland itself) or secondary (when a lack of secretion of corticotropin-releasing hormone [CRH] from the hypothalamus or of adrenocorticotrophic hormone [ACTH] from the pituitary leads to hypofunction of the adrenal cortex). The condition can be further classified as congenital or acquired. In the group of 0-6 years of age, congenital primary AI is the most common aetiology. It may occur as a result of adrenal hypoplasia or hyperplasia.

Congenital adrenal hyperplasia (CAH) is the most common congenital genetic endocrine disorder and results from mutations in the cortisol synthesis pathway in the adrenal glands. Mutations in the 21-hydroxylase gene, a key enzyme in cortisol and aldosterone synthesis, account for 95% of cases. 21-hydroxylase deficiency has an incidence of 1:12,000 live births for severe mutations causing classic CAH, which manifests in the neonatal period. In CAH, failure in cortisol synthesis results in reduced cortisol feedback and consequently increased pituitary ACTH release, which promotes over-secretion of 17-hydroxyprogesterone (17-OHP), progesterone and adrenal androgens. This results in androgen excess that clinically manifests with disordered sex development in girls, precocious pseudopuberty, and short stature, and in adulthood with hirsutism in females and fertility problems in both sexes.

With proper treatment and compliance, patients with cortisol deficiency can live a normal life span without limitations. However, the prognosis for an untreated patient is poor. Death is a common outcome, usually from hypotension or cardiac arrhythmia secondary to hyperkalaemia, unless replacement steroid therapy is begun. Glucocorticoid replacement in CAH aims both to replace cortisol and prevent ACTH-driven androgen excess (Dauber et al., 2010). This is challenging, since therapy aiming to normalise ACTH and reducing androgen levels results in excess glucocorticoid exposure with associated complications including short stature, obesity, hypertension and an adverse metabolic profile. Striking the balance between too much and too little glucocorticoid treatment is especially difficult as currently available glucocorticoid formulations cannot replicate the circadian rhythm of cortisol secretion and are not formulated for the paediatric population. CAH is a life-long chronic disorder. In childhood, treatment focuses on issues of gender assignment, genital surgery, optimisation of growth and pubertal development. Priorities change with increasing age, focusing on fertility in early adult life and prevention of metabolic syndrome and osteoporosis in middle and older age, respectively.

Other causes for AI besides CAH include congenital adrenal hypoplasia, lipoid adrenal hyperplasia and hypopituitarism – all of which are extremely rare.

5.2 Preclinical Experience

Hydrocortisone is a naturally-occurring glucocorticoid hormone secreted by the healthy adrenal cortex and the goal of therapy in AI is to replace this hormone to physiological levels. Such replacement therapy has been a routine part of medical care in both adults and children for more than 50 years and its safety profile is well understood.

All the excipients used in Infacort® immediate release granules are standard materials normally used in pharmaceutical drug products. All are the subject of European Pharmacopeia and/or

United States Pharmacopeia/National Formulary (NF) Monographs and have been used in pharmaceutical products worldwide over many years. Additional information on these materials may be obtained from 'The Handbook of Pharmaceutical Excipients – 7th Edition' (2012). Therefore no preclinical studies were performed for Infacort®.

5.3 Clinical Experience

The pharmacokinetic (PK) profile of Infacort® immediate release granules has been characterised in study Infacort 001 (EudraCT number: 2013-000260-28). This randomised, crossover study was undertaken in dexamethasone-suppressed healthy male adult subjects to determine the bioequivalence of 10 mg Infacort® compared with a 10 mg dose of immediate release hydrocortisone and to evaluate the dose-proportionality of Infacort® at doses of 0.5, 2, 5 and 10 mg. Each dose of investigational medicinal product (IMP) (Infacort® granules 0.5 mg, 2 mg, 5 mg, 10 mg and hydrocortisone 10 mg tablet) was administered to each of 16 subjects in a randomised crossover manner over 5 treatment periods. Each subject received their scheduled treatment at approximately 07:00 hours, in a fasted state. They also received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22:00 hours on the night before, and at approximately 06:00 and 12:00 hours on the day of treatment. PK samples were taken to determine serum cortisol levels pre-dose and at regular intervals for up to 12 hours post-dose and used to determine the maximum plasma concentration (C_{max}), the time at which C_{max} occurs (T_{max}), half-life ($t_{1/2}$), the area under the plasma concentration versus time curve (AUC) from the time of dosing to the time of the last observed concentration (AUC_{0-t}) and the AUC extrapolated to infinity from dosing time, based on the last observed concentration (AUC_{0-inf}). To establish bioequivalence, the geometric least square (LS) mean 90% confidence interval (CI) for the ratios of C_{max} , AUC_{0-t} and AUC_{0-inf} were determined for Infacort® and hydrocortisone. Bioequivalence was demonstrated for the 10 mg Infacort® compared with a 10 mg dose of immediate release hydrocortisone, and over the 0.5 mg to 10 mg Infacort® dose range, C_{max} , AUC_{0-t} and AUC_{0-inf} were shown to increase in a linear fashion.

A second study, Infacort 002 (EudraCT number: 2013-000259-42) has been performed in dexamethasone-suppressed healthy adults to show the bioequivalence of 20 mg Infacort® compared with a 20 mg dose of immediate release hydrocortisone. Each treatment (Infacort® 20 mg, hydrocortisone tablets 20 mg, and intravenous hydrocortisone 20 mg) was administered as a single dose to each of 14 healthy male subjects in a partially randomised crossover manner over 5 treatment periods (1 treatment per period). In treatment period 1, no treatment was administered and endogenous cortisol production was measured. In subsequent treatment periods, each subject also received 1 mg dexamethasone (to suppress endogenous cortisol production) at approximately 22:00 hours on Day 1, and at approximately 06:00 hours and 12:00 hours on Day 2. Preliminary data from this study indicate that oral Infacort® and hydrocortisone tablets are, respectively, approximately 87% and 97% bioavailable when compared to the reference intravenous hydrocortisone injection. Oral Infacort® and hydrocortisone tablets were considered bioequivalent, with geometric LS mean 90% CI for the ratios of C_{max} , AUC_{0-t} and AUC_{0-inf} falling within 80 - 125. T_{max} was also similar between the 2 formulations, indicating no important differences in the rate of absorption. The preliminary data from this study again demonstrates the bioequivalence of Infacort® and hydrocortisone – this time at a dose of 20 mg. There were no notable adverse events (AEs), and Infacort® appeared palatable.

At physiological replacement doses there are no major reported side-effects of hydrocortisone therapy. The doses of hydrocortisone in the Infacort 001 and Infacort 002 studies produce concentrations that encompass the physiological range. Immediate release oral tablets of hydrocortisone have been approved and marketed worldwide (including in all European Union [EU] countries) for more than 20 years.

5.4 Rationale

As the underlying pathology is, in nearly all cases, untreatable, the mainstay of treatment for AI in the paediatric population is replacement therapy using hydrocortisone which has been practiced since the late 1940s. The major issue is that there is no evidence base for the use of current formulations of hydrocortisone in neonates. For neonates and infants there is no licensed preparation available that provides the appropriate physiological dose in a formulation that can be given to neonates and infants. Currently available hydrocortisone preparations are either for intravenous or adult use. Neonatologists and local pharmacists have to grind hydrocortisone tablets to powder and estimate the dose to be encapsulated. Parents are then supplied with capsules containing crushed tablets. However, there is no formal quality control. A recently undertaken analysis in Berlin showed that nearly 25% of the batches failed to meet the acceptance criteria of mass and content uniformity based on the European Pharmacopoeia (**Figure 1**) (Neumann et al., 2017), possibly explaining poor control of congenital adrenal hyperplasia in some small children and neonates (Kauzor et.al., 2014).

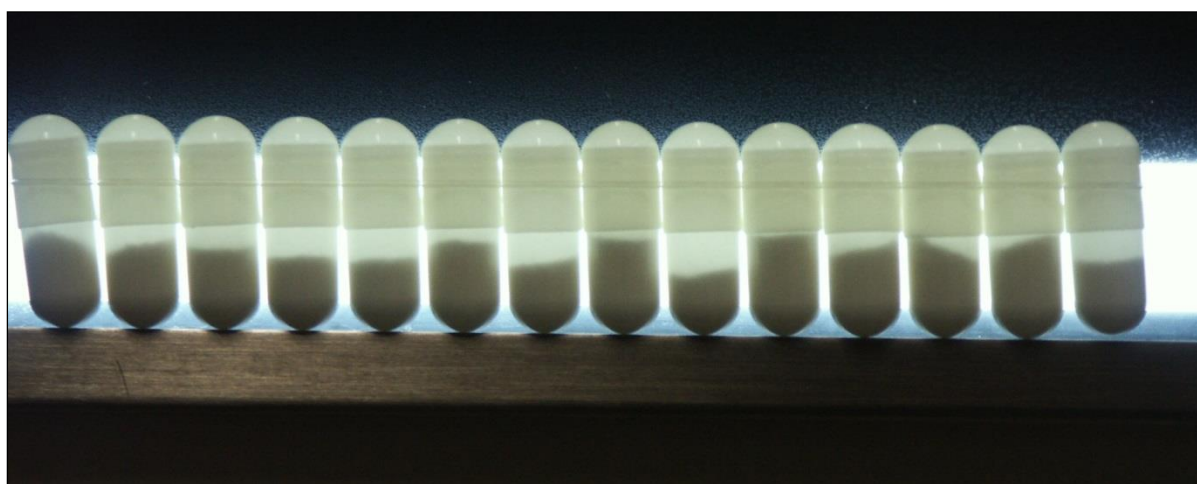


Figure 1: Capsules Containing Hydrocortisone, Individually Prepared for a Subject (Note Variation in Dose Between Capsules)

Young children and neonates are therefore at risk for under-treatment, resulting in adrenal crisis, or over-treatment which may lead to impairment of growth.

Infacort® is a new formulation of hydrocortisone that is available in a wide range of doses to meet the dosing needs of neonates and infants suffering from AI. The taste is also masked to avoid the bitter characteristic taste of hydrocortisone. The microparticulate formulation is especially suitable for young children in need of hydrocortisone replacement therapy.

Study Infacort 003 evaluated PK, safety and tolerability of a single dose of Infacort® according to the agreed Paediatric Investigation Plan (PIP). This study Infacort 004 aims to extend the observations to look at long-term treatment effects.

5.5 Hypothesis

The administration of Infacort® to infants, neonates and children who have completed study Infacort 003 is safe and produces the required effects following long-term administration.

5.6 Risk/Benefit Assessment

The IMP used is hydrocortisone, which is a well understood replacement therapy for subjects with AI. The safety profile of hydrocortisone is well characterised. This formulation of hydrocortisone is produced specifically for young children, for whom there is no licensed preparation of oral hydrocortisone. Infacort® has already been assessed in adult healthy subjects, and found to be bioequivalent with hydrocortisone tablets, and to have acceptable taste properties. Subjects in this study will already have received a single dose of Infacort® in study Infacort 003, and this will have been shown to be adequately absorbed. This study therefore poses a minimal risk to the involved subjects.

All emerging safety data will be assessed for any signal of safety problems on an ongoing basis. An analysis of safety and biochemical disease control will be undertaken and overseen by an Independent Data Monitoring Committee (IDMC) on a yearly basis (this may be abbreviated in the early years when there is insufficient data to undertake a full analysis). The IDMC terms of reference and supplementary charter will be provided as a separate document.

The potential benefits of the new treatment include precise dosing, avoiding the long-term consequences of under or over-treatment, or varying treatment efficacy, and palatable treatment that is easily swallowed, which outweigh the risks of this study being performed in children.

6 Study Objectives

6.1 Primary Objective

- To gather data on the long-term safety of Infacort® in subjects completing study Infacort 003.

6.2 Secondary Objectives

- To gather data on the effects of Infacort®.

7 Study Endpoints

7.1 Primary Endpoint

- Nature and occurrence of serious adverse events (SAEs) and AEs observed throughout the study.

7.2 Secondary Endpoints

- Standard deviation score (SDS) for height and weight.
- Cortisol (all subjects) and adrenal androgen levels (17-OHP, androstenedione [A4], testosterone) in CAH subjects only.

8 Study Design

This is a Phase 3, open-label, single-group, non-randomised, observational study of the safety and biochemical disease control of Infacort® in neonates, infants and children with AI who have completed study Infacort 003 (EudraCT number 2014-002265-30). All subjects who have satisfactorily completed study Infacort 003 will be offered the opportunity to participate in study Infacort 004 at or after their final visit of study Infacort 003. Subjects will receive the usual clinically-appropriate dose (since bioequivalence has been demonstrated with conventional hydrocortisone), as determined by the Investigator, which will be administered according to usual clinical practice – generally 3 or 4 times a day. Subjects can continue to be treated in this study until they meet the study withdrawal criteria (see Section 11), Infacort® is granted a marketing authorisation (and so is available commercially², which is expected within 2 years of initiation of this study), Infacort® is refused a marketing authorisation, or the Sponsor decides to discontinue the study.

The standardised protocol for follow-up will include:

- Initial visit
- Monthly visits for the first 2 months of treatment
- Thereafter visits every 3 months
- Final visit

The study will be conducted in up to 24 subjects from the Infacort 003 study requiring replacement therapy for AI due to either CAH, primary adrenal failure or hypopituitarism. The primary site will be Charité-Universitätsmedizin Berlin, CVK. However, some subjects participating in Infacort 003 may have been transferred from remote sites. Should their parents/carers and clinician agree to participation in Infacort 004, the previous remote sites will be involved as study centres in this study (or, if agreeable, the subjects may be cared for at Charité-Universitätsmedizin Berlin for the purposes of the study). In some agreed cases, whilst the subject is cared for by Charité-Universitätsmedizin Berlin for the purposes of the study, it may be necessary for the Investigator at Charité-Universitätsmedizin Berlin to conduct the study visits at the subject's local hospital. Detailed guidelines to address the process for enrolment of such subjects and the performance of study procedures at remote sites are included in Appendix 6 and will be submitted to the Independent Ethics Committee (IEC) and the German Competent Authority 'Bundesoberbehörde' (BfArM).

Parents/carers will be provided with the informed consent document at least 24 hours prior to enrolment of their child in the study. Children aged over 3 years old will be informed about their involvement in the study in the presence of their parents/carers. For each visit, care will

² At the time of submission of this amendment (protocol version 4.0), Infacort® is the subject of an ongoing Marketing Authorisation Application procedure. For clarity, the end of study visits for each subject will occur after Infacort® is commercially available.

be taken to note the time of any blood sampling, and the time and dose of the previous administration of glucocorticoid.

8.1 Assessments

Subjects successfully completing study Infacort 003 are eligible to enter this Infacort 004 study. The study procedures to be conducted for each subject enrolled into the Infacort 004 study are detailed in **Table 1**:

Table 1: Schedule of Study Assessments

	Initial Visit	Interim Visits¹	Final Visit
Written informed consent ²	X		
Medical history/current medical status ³	X		
Physical examination	X	X	X
Height/length	X	X	X
Weight	X	X	X
Vital signs ⁴	X	X	X
Inclusion/exclusion criteria	X		
Previous/concomitant medication ⁵	X	X	X
Infacort® administration	X ⁶	X	
Infacort® education for parents/carers	X		
Problems associated with administration/dosing	X	X	X
Tanner development stage	X	X	X
SAEs and AEs ⁷		X	X
Blood sampling ⁸ (electrolytes, renin, haematocrit and any additional cortisol data)	X	X	X
Dried blood spot sampling ⁹	X	X ¹⁰	X
Incidence of adrenal crisis		X	X
Incidence of sick day rules		X	X
End of study information ¹¹			X

¹ Interim visits monthly for the first 2 months of treatment then every 3 months.

² Written informed consent must be provided at least 24 hours prior to enrolment.

³ Medical history from Infacort 003 will be used, plus any changes since the subject was enrolled in the Infacort 003 study.

⁴ Blood pressure (where possible), heart rate and temperature.

⁵ To include current adrenal replacement therapy at the initial visit

⁶ First dose administered by the parent/carer in the presence of the Investigator at the initial visit.

⁷ AEs will be recorded from the time of the first intake of Infacort® in this study until the final visit. SAEs will be recorded from the time of the first intake of Infacort® in this study until 7 days after the last dose of Infacort®. Any SAEs experienced after this 7-day period should only be reported if the Investigator suspects a causal relationship to Infacort®.

⁸ Where taken as part of routine clinical care (normally once a year). The time of the blood sampling and the time of the last glucocorticoid dose will be recorded.

⁹ The time of blood sampling will be noted, as well as the time and dose of the previous administration of glucocorticoid. Where possible the blood spot sample should be taken in the morning.

¹⁰ For the first 2 months of treatment and then 6-monthly thereafter unless required after 3 months.

¹¹ At final visit or at withdrawal from the study.

Initial Visit:

The primary site will be Charité-Universitätsmedizin Berlin, CVK. However, some subjects participating in Infacort 003 may have been transferred from remote sites. Should their parents/carers and clinician agree to participation in Infacort 004, the previous remote sites will be involved as study centres in this study (or, if agreeable, the subjects may be cared for at Charité-Universitätsmedizin Berlin, for the purposes of the study). In some agreed cases, whilst the subject is cared for by Charité-Universitätsmedizin Berlin for the purposes of the study, it may be necessary for the Investigator at Charité-Universitätsmedizin Berlin to conduct the study visits at the subject's local hospital. Detailed guidelines of the processes in such cases are included in Appendix 6.

On completion of Visit 4 of study Infacort 003, subjects can undergo the initial visit for this Infacort 004 study. Date of birth, gender, race/ethnicity, and medical history will be retrieved from Infacort 003 data. Other assessments at this visit include:

- Informed consent (parents/carers will be provided with the informed consent document at least 24 hours prior to enrolment of their child in this study)
- Changes in medical history/current medical status since enrolment in the Infacort 003 study
- Physical examination
- Height/length
- Weight
- Body mass index (BMI) and body surface area (BSA) (derived)
- Vital signs
 - Blood pressure (if possible)
 - Heart rate
 - Temperature
- Compliance with inclusion/exclusion criteria
- Tanner development stage
- Previous and concomitant medication (including current adrenal replacement therapy)
- Dried blood spot sampling (cortisol [all subjects], and 17-OHP, A4, testosterone [CAH subjects only]). Where possible the blood spot sample should be taken in the morning. The time of blood sampling and the time and dose of the previous glucocorticoid administration will be recorded.
- Blood sampling (electrolytes, renin, haematocrit, and any additional cortisol data) if taken as part of routine clinical care (the time of blood sampling and the time of the last glucocorticoid dose will be recorded).
- Infacort® administration education for parents/carers
- First dose of Infacort® administration given by the parent/carer in the presence of the Investigator. Details of the dose and time of eating will be recorded in the case report form (CRF)
- Problems associated with administration/dosing - entire or incomplete dosing will be recorded in the CRF

Interim Visits:

- Physical examination
- Height/length
- Weight
- BMI and BSA (derived)
- Vital signs

- Blood pressure (if possible)
 - Heart rate
 - Temperature
- Concomitant medication
- SAEs and AEs, including application of sick day rules and adrenal crises
- Dried blood spot sampling (cortisol [all subjects], and 17-OHP, A4, testosterone [CAH subjects only]) every 6 months following the first 2 months of treatment, unless required after 3 months. Where possible the blood spot sample should be taken in the morning. The time of blood sampling and the time of the last glucocorticoid dose will be recorded.
- Blood sampling (electrolytes, renin, haematocrit, and any additional cortisol data) where taken as part of routine clinical care (normally once a year). The time of blood sampling and the time of the last glucocorticoid dose will be recorded.
- Tanner development stage
- Dose of Infacort®
- Problems associated with administration/dosing

Final Visit:

- Physical examination
- Height/length
- Weight
- BMI and BSA (derived)
- Vital signs
 - Blood pressure (if possible)
 - Heart rate
 - Temperature
- Concomitant medication
- Problems associated with administration/dosing
- SAEs and AEs, including application of sick day rules and adrenal crises
- Dried blood spot sampling (cortisol [all subjects], and 17-OHP, A4, testosterone [CAH subjects only]). Where possible the blood spot sample should be taken in the morning. The time of blood sampling and the time of the last glucocorticoid dose will be recorded.
- Blood sampling (electrolytes, renin, haematocrit, and any additional cortisol data) if taken as part of routine clinical care (the time of blood sampling and the time of the last glucocorticoid dose will be recorded)
- Tanner development stage
- End of study information (completion/withdrawal status etc.).

8.2 Repeat Evaluation or Additional Assessments

Should it become necessary to repeat an evaluation (e.g., vital signs), the results of the original and the repeat evaluation will be captured. The additional assessment should be entered in the 'Unscheduled Visit' page provided in the CRF.

8.3 Demographics

These include date of birth, gender, race, height/length and weight. Date of birth, gender and race will be retrieved from the Infacort 003 data.

8.4 Relevant Medical History/Current Medical Status

Relevant medical history and current medical conditions will be recorded in the CRF at the initial visit. Information on medical history can be used from the Infacort 003 study, but any changes since enrolment in the Infacort 003 study must be noted.

8.5 Previous and Concomitant Medication/Treatment

At the initial visit, the Investigator will record any medications and significant non-drug therapies the child took before the first intake of Infacort® in this study as well as any medications that are currently being taken (i.e. concomitant medications). Any changes in concomitant medications will be recorded, with other adrenal replacement therapies being recorded separately in the CRF. Medication entries should specify the generic name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

8.6 Physical Examination

This evaluation will include an examination of skin, nose and throat region, lungs, heart, abdomen, back, genital status and basic nervous system evaluation. Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present **prior to** the start of Infacort® treatment must be included in the relevant medical history/current medical status section of the CRF. Significant findings made **after** the start of Infacort® treatment which meet the definition of an AE must be recorded in the Adverse Event CRF summary page.

8.7 Blood sampling

A dried blood spot sample will be collected at the initial and final visits, every month for the first 2 months of treatment and thereafter every 6 months, unless required after 3 months. Where possible the blood spot sample should be taken in the morning but the exact time of the sample should be recorded. The dried blood spots will be analysed for multi-steroids, including cortisol (all subjects), and 17-OHP, A4, and testosterone (CAH subjects only), by the laboratory at Charité-Universitätsmedizin Berlin (details of collection methodology and analytes to be tested are provided in Appendix 1). Electrolytes, renin, haematocrit, and any additional cortisol data will also be collected where collected routinely by the local laboratory as part of the routine clinical care (normally once a year). The results of all these analyses will be included in the database. These data may be merged with that collected in the Infacort 003 study for population PK analyses. The amount of blood collected at each visit will be approximately 2 mL. Blood sampling performed for the purpose of the study and not as part of routine clinical care (e.g. dried blood spot samples) requires 75 – 80 µl of blood for each additional sample. The additional blood volumes pose no health risk for the subjects. Blood spots will be collected from either venous or capillary sampling.

The taking of venous blood samples poses no additional health risk for the subjects and does not provide any additional burden for the subject as study related venous sampling is limited to routinely performed venous punctures in the management of the subject's condition. Where venous blood samples are taken as part of routine clinical care the blood spot will also be collected from venous sampling.

8.8 Drug Administration Record

The dose of Infacort® prescribed and dispensed to the subject and all changes during the study must be recorded on the dosage administration record section of the CRF. A diary card will be provided so that parent/carer can record any missed doses etc. between visits. Any problems associated with administration or dosing (e.g. capsule spilt etc.) should also be recorded.

8.9 Infacort® Education for Parents/Carers

Since the parents/carers will be administering the Infacort® to the subjects at home, they will be trained how to administer the study medication by the Investigator or Study Nurse during their initial visit. They will also be given an instruction sheet to take home with them for reference, which will include written instructions on the dose to be taken from the clinician. They will also be instructed how to complete the diary card, and they will be asked to bring this along to all visits.

8.10 Tanner Development Stage

The Tanner Development Stages are shown in Appendix 2. At each visit the Investigator will record the development of the subject using this scale.

8.11 End of Study Information

Information on subject completion or withdrawal from the study and the reason for withdrawal from the study will be recorded on the Study Completion CRF page. Study completion evaluations must also be performed when a subject prematurely withdraws from the study for whatever reason. In the case of death, the cause of death must be recorded.

8.12 Safety Assessments

8.12.1 Vital Signs and Body Measurements

Body height/length (cm) and body weight (kg to 1 decimal place) will be obtained at each visit. Systolic and diastolic blood pressure (mmHg) (if possible), heart rate (beats/min) and body temperature (°C) will also be assessed at each visit. Blood pressure should be assessed using the same arm and the same measurement conditions for each time of determination.

8.12.2 Adverse Events

The collection of AEs is described in Section 12.

AEs will be recorded from the time of the first intake of Infacort® until the final visit. A diary card will be provided so that parents/carers can record any relevant events between visits. In particular, events associated with dosing (e.g. choking) should be noted. These diary cards will be discussed with the Investigator at each visit and any relevant information will be transferred into the CRF.

8.13 Sick Day Rules

All subjects will be supplied with “Sick day rules” (an example is provided in Appendix 3). When these rules are implemented for a subject, the number of days they are used must be documented.

8.14 Assessment Windows

Windows for the following assessment times are acceptable based on logistical and operational considerations:

- Interim visit (± 10 days)
- Final visit (± 10 days)

If a visit needs to be postponed for more than 10 days (i.e. holidays), 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.

8.15 Estimated Study Duration

Subjects will enter this study following completion of the Infacort 003 study. Parents/carers will be provided with the informed consent document at least 24 hours prior to enrolment of their child in the study. The start of the study will be considered as the date of the signed informed consent of the first subject in this study. Subjects can continue to be treated in this study until they meet the study withdrawal criteria (see Section 11), Infacort® is granted a marketing authorisation (and so is available commercially, which expected within 2 years of initiation of this study), Infacort® is refused a marketing authorisation, or the Sponsor decides to discontinue the study.

8.16 Post-Study Management

The conclusion of the study is defined as the last visit of the last subject. Each subject's study participation ends when all planned study procedures have been completed (after the final visit). The subjects may continue their usual therapy with hydrocortisone after the last intake of Infacort® or with Infacort® if commercially available.

9 Subject Population

9.1 Number of Centres

The primary site will be Charité-Universitätsmedizin Berlin, CVK, since this site enrolled all of the subjects into the Infacort 003 study. However, some subjects participating in Infacort 003 may have been transferred from remote sites. If the parents/carers and clinician of these subjects agree to participation in Infacort 004, the previous remote sites will be involved as study centres in this study (or, if agreeable, the subjects may be cared for at Charité-Universitätsmedizin Berlin for the purposes of the study). In some agreed cases, whilst the subject is cared for by Charité-Universitätsmedizin Berlin for the purposes of the study, it may be necessary for the Investigator at Charité-Universitätsmedizin Berlin to conduct the study visits at the subject's local hospital. The procedure for this is detailed in Appendix 6.

9.2 Number of Subjects

The subjects included in this clinical trial will not be selected with regard to their sex, since no gender specific differences concerning efficacy and safety of the IMP are expected (see GCP-V § 7 (2) No. 12). There are no gender related effects of hydrocortisone which could influence the outcome of the study.

A maximum of 24 subjects will be enrolled in study Infacort 004. The number of subjects in this study will be determined by the number wanting to continue to receive Infacort® after they complete study Infacort 003 (which will recruit up to a maximum of 24 subjects). The Investigator in the Infacort 003 study will ensure that all subjects treated in study Infacort 003 are invited to participate in this Infacort 004 study. No additional exclusions to those detailed in Section 9.4 will be applied by the Investigator.

Subject selection is to be established by checking through all inclusion/exclusion criteria at the initial visit. A record of this check (e.g. inclusion/exclusion checklist) must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a subject from enrolment into the study unless it is temporary – then subjects may be entered when the temporary exclusion criterion resolves.

9.3 Inclusion Criteria

Subjects successfully completing study Infacort 003, whose inclusion criteria were:

1. Male and female children less than 6 years of age.
2. A diagnosis of AI as confirmed by an inappropriately low cortisol usually with other supporting tests.
3. Receiving appropriate adrenocortical replacement therapy (hydrocortisone with/without fludrocortisone).
4. Adequately hydrated and nourished.

In addition, the parents/carers must be able to understand and give written Informed Consent (according to AMG §40 (1) 3b) for this extension study.

9.4 Exclusion Criteria

1. Clinically evident acute AI (adrenal crisis) (Note: the subject can be re-evaluated for eligibility once the episode is over).
2. Inability of the child to take oral therapy.
3. Subjects with clinical signs of acute infection or fever on inclusion (Note: the subject can be re-evaluated for eligibility once the episode is over).
4. Any surgical or medical condition that in the opinion of the Investigator may place the subject at higher risk from his/her participation in the study.
5. Parents/carers of subjects unwilling to consent to saving and propagation of pseudonymised medical data for study reasons
6. Subjects who are in a dependent relationship with the Investigator or the Sponsor

9.5 Justification for the Inclusion of Minors and Persons Unable to Consent

Although children <6 years of age, infants and neonates with AI are currently treated with crushed hydrocortisone tablets, no cortisol replacement therapy has ever been officially licensed for these age groups. Whilst hydrocortisone is universally accepted as an appropriate replacement therapy in AI, the availability of current oral products only as solid tablets significantly impairs its usefulness in neonates, infants and young children. Crushed tablets are currently used, leading to imprecise dosing and poor palatability due to the bitter taste of hydrocortisone. We are therefore developing an age-appropriate oral formulation of hydrocortisone which will allow for optimising therapy in the proposed age-group, since a range of microparticulate doses will be available, which will be suitably taste masked.

10 Study Medication and Administration

10.1 Randomisation, Numbering and Blinding

This is an open-label, single-group, non-randomised, observational study and therefore no blinding or un-blinding procedures are required. Each subject is uniquely identified in the study by the subject number allocated to them in study Infacort 003. This subject number is the unique identifier throughout the study and will not be reused.

10.2 Description and Handling of Infacort®

10.2.1 Formulation

Infacort® is formulated as immediate release multiparticulate granules filled in a hard capsule. The capsule contents (multiparticulate granules) are either administered directly onto the top, and towards the back, of the child's tongue or the granules can be sprinkled onto a spoonful of yoghurt, fruit purees (e.g. apple sauce) or fruit mousses immediately before being administered to the child. The granules can also be washed down with water, breast milk, formula milk or whole milk following administration. The hard capsule itself is a carrier and not for consumption. Infacort® is available in dose strengths of 0.5, 1.0, 2.0 and 5.0 mg hydrocortisone and presented in size 00el hard capsules.

All excipients used in Infacort® immediate release granules are the subject of European Pharmacopeia and/or United States Pharmacopeia/NF Monographs, and have been used in pharmaceutical products worldwide over many years. Infacort® immediate release granules have been assigned the unique product identifier (UPI) of 997249.

10.2.2 Packaging and Labelling

Infacort® is supplied as 0.5, 1.0, 2.0 and 5.0 mg dose strengths. Infacort® capsules are contained within either a PVC/PE/PVdC blister pack sealed with aluminium lidding foil or a high-density polyethylene (HDPE) bottle sealed with a polypropylene (PP) lid. Each blister pack contains 10 capsules of the same dose strength and 10 blister packs are packaged in a cardboard carton to produce a 100-count pack of each dose strength. Each bottle contains 40 capsules of the same dose strength. The Sponsor will supply the pharmacy at the study sites with cardboard cartons or bottles of each dose strength for dispensing according to the appropriate dose determined by the Investigator (see Section 10.3).

Infacort® will be appropriately labelled in accordance with Annex 13, Rev 1 (manufacture of IMPs) of the EC guide to Good Manufacturing Practice.

All supplies of Infacort® will be labelled with a minimum of the protocol number, subject number, pharmaceutical dosage form (including product name, strength and quantity of dosage units), directions for use, storage conditions, expiry date, batch number, the statements 'For clinical trial use only', Investigator name and the Sponsor's name and address information.

The documentation supplied with the Infacort® IMP will make it possible to retrace the composition and pharmaceutical quality of the product.

10.2.3 Storage

Infacort® will be stored in a secure, temperature-controlled pharmacy at a temperature not exceeding 25°C. Infacort® does not require cold chain transportation, and the drug product has an established stability profile that demonstrates the drug product remains stable at ambient storage conditions and is stable at an accelerated temperature of 40°C over 1 month. However, Infacort® will always be shipped at a controlled temperature not exceeding 25°C. Temperature monitors, included with the Infacort® shipments, will be downloaded by the pharmacist and provided to the Sponsor to confirm that the transportation conditions are acceptable, i.e. to ensure that the Infacort® is maintained within the established temperature range in accordance with the labelled storage conditions. Parent/carer should be instructed to ensure that Infacort® is stored in accordance with the labelled storage conditions. The Sponsor must be notified of any known temperature excursion during the clinical trial in order to assess the impact and provide supportive documentation as necessary. Note: see Appendix 6 for shipment of IMP to remote sites.

10.2.4 Accountability

All used (empty blister packs/bottles) and unused Infacort® will be returned to the pharmacy, where the amount dispensed and the amount returned will be recorded. Following the Sponsor's approval, any unused Infacort® will either be returned to the supplier or to the Charité Pharmacy (where it will be destroyed on site and a certificate of destruction provided).

10.3 Dosage and Administration of Infacort®

Infacort® is supplied as 0.5, 1.0, 2.0 and 5.0 mg dose strengths. The normal clinically-appropriate dose, based on standard individualised treatment, will be administered according to usual clinical practice (since Infacort® has been shown to be bioequivalent to conventional hydrocortisone) – generally 3 or 4 times a day.

The drug is presented in a capsule. **The capsule is not to be consumed, it is only a container for the drug.**

Immediately prior to administration of Infacort®, the capsule will be opened and the entire contents (i.e. drug granules) administered. The granules will be administered either:

1. directly onto the top and towards the back of the child's tongue and washed down immediately with fluid (water, breast milk, formula milk, or whole milk), or
2. administered onto the top and towards the back of the child's tongue using a spoon and washed down immediately with fluid (water, breast milk, formula milk, or whole milk), or
3. Sprinkled onto a spoonful of yoghurt, fruit purees (e.g. apple sauce) or fruit mousses immediately before being administered to the child. The granules can also be washed down with water, breast milk, formula milk or whole milk following administration.

Training on administration of the study medication will be given to the parents/carers at the initial visit by the Investigator or Study Nurse. The first dose at the initial visit will be administered by the parent/carer under the supervision of the Investigator or Study Nurse, with subsequent doses administered by the parents/carers at home. Administration of incomplete doses (e.g., spilling of granules during administration in excess of 10%) should be recorded by the parents/carers in the diary cards and then transcribed into the CRF by the site staff. Sufficient drug will be dispensed by the pharmacy in case of spillages prior to administration.

Any case of incomplete administration of the study medication must be recorded in the diary card. If it is estimated that >25% of the study medication was not swallowed (i.e. spat out) the dose should be repeated, with the repeat administration recorded in the diary card.

If vomiting occurs within 30 minutes of administration of Infacort® the dose should be repeated, with the repeat administration recorded in the diary card. Standard care should also be implemented. The event should be recorded on the diary card and recorded as an AE, if appropriate. In the case of repeated vomiting, the sick day rules apply (an example of which is detailed in Appendix 3).

10.4 Permitted Concomitant Medications/Treatments

Throughout the study the subjects will continue to take all their regular treatments, with the exception of hydrocortisone, which will be replaced with Infacort®. All prior and concomitant medications must be recorded on the CRF. A diary card will be provided to the parents/carers so that any changes to concomitant medications between visits can be recorded.

10.5 Overdose

In the event of an overdose, the parent/carer should immediately contact the Investigator or Study Nurse for advice. There is no antidote available for Infacort®.

11 Subject Withdrawal and Replacement

11.1 Early Withdrawal from the Study

Individual subjects may be withdrawn from the study for any reasons and without prejudice to further treatment including:

- Withdrawal of consent (by the parent/carer)
- New medical conditions that may compromise the safety of the subject, for example any condition that impairs the subject's ability to swallow, which may preclude oral medication.
- Decision of the Investigator if he/she considers the subject's health may be compromised by remaining in the study. The investigator may consider this if there are more than 3 episodes of sick day rules without reasonable explanation (eg infection, fever, trauma etc), or two or more episodes of Addisonian Crisis without reasonable explanation (eg infection, fever, trauma etc).

11.2 Premature Termination of the Clinical Study

The study may be terminated at any time in the event of:

- Emerging data from the study suggests an unfavourable risk-benefit analysis.
- New scientific evidence provided during the study that could affect the subject's safety (benefit-risk analysis no longer positive).
- Request of the Sponsor, the IDMC or regulatory agency.

11.3 Replacement of Withdrawn Subjects

Any subject who is withdrawn from the study will not be replaced.

11.4 Intercurrent Illness or Need for Temporary Increase in Dose

Details of the management of the subject during illness or when a temporary increase in dose is needed are provided in Appendix 3.

12 Adverse Events and Toxicity Management

The occurrence of AEs events should be sought by indirect questioning of the parents/carers and child (if possible) at each visit. AEs may also be detected when they are volunteered by the parent/carer or child during or between visits or through diary cards, physical examination, vital signs or other assessments. During the study, the parents/carers will be instructed to observe their child carefully for any unusual/abnormal signs and symptoms which may constitute an

AE. Details must be recorded in the diary card by the parent/carer and will be discussed with the Investigator during each visit.

12.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE could be any diseases, signs or symptoms (including an abnormal laboratory finding) which occurs or worsens after starting the study drug even if the event is not considered to be related to study drug. This includes any newly occurring event or previous conditions that have increased in severity or frequency since the administration of the study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

12.2 Adverse Event Collection

AEs will be recorded from the time of first intake of Infacort® until the final visit of the study. Clinical events which started before the first intake of Infacort® or that are ongoing AEs from study Infacort 003, will be recorded as medical history or concurrent disease. SAEs will be recorded from the time of first intake of Infacort® in this study until 7 days following the last administration of Infacort®. Any SAEs experienced after this 7-day period will only be reported to the Sponsor if the Investigator suspects a causal relationship to Infacort®. If any SAEs are ongoing from study Infacort 003, the subject should not start treatment in this extension study until the SAE has resolved or stabilised.

Details of any AEs will be collected, including details of date of onset, end date, frequency, severity, seriousness, relationship to Infacort®, action taken and outcome. Any AE will be followed, whenever possible, until it returns to the baseline condition or becomes stable with no further change expected. In the event of any abnormalities considered to be clinically significant by the Investigator, subjects will be followed up with appropriate medical management until values are considered to be clinically acceptable and no further changes can be expected. Referral or collaborative care will be organised if required.

12.3 Reporting of Adverse Events

All individual AEs should be evaluated by the Investigator and recorded in the CRF.

12.3.1 Diagnoses vs. Signs/Symptoms

Each AE should be recorded to represent a single diagnosis. Accompanying signs or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as the AE.

12.3.2 Pre-Existing Conditions

Pre-existing conditions that are present before the intake of Infacort® in this study (including any ongoing AEs from study Infacort 003) are considered concurrent medical conditions and should NOT be recorded as AEs. These findings should be recorded on the current medical status CRF page. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators

should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of...”).

12.3.3 Pre-Planned Surgeries or Procedures

Pre-planned procedures (surgeries or therapies) that were scheduled prior to the start of the study are not considered AEs. However, if a pre-planned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE.

12.3.4 Elective Surgeries or Procedures

Elective procedures performed where there is no change in the subject’s medical condition should not be recorded as AEs, but should be documented in the subject’s source documents.

12.3.5 Overdose

Cases of drug overdose without manifested events are NOT considered AEs, however, such events should be noted in the CRF.

12.3.6 AEs of Special Interest

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 considered to be AEs of special interest and should be recorded as such. In addition, any occurrence of adrenal crisis must be recorded as an AE of special interest. Similar information to that collected for SAEs will be collected for such events (however, the event only needs to be reported as an SAE if it meets the criteria detailed in Section 12.7).

12.4 Assessment of Adverse Event Severity

The following guidelines for rating severity of AEs will be used:

Mild:

Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms may be transient, disappearing during continued treatment with study medication.

Moderate:

Discomfort enough to cause interference with usual activities; the study medication may have been interrupted.

Severe:

Incapacitating with inability to do usual activities; signs and symptoms may be of systemic nature or require medical evaluation; the study drug may have been stopped, and treatment for the event may be required.

The term “severe” is often used to describe the intensity of a specific event, as in mild, moderate, or severe myocardial infarction; the event itself, however, may be of relatively minor

medical significance, such as severe headache. This is not the same as serious, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

12.5 Assessment of Adverse Event Causality/Relatedness

All AEs will be assigned one of the following assessments of causality:

- Unrelated
- Related

All AEs judged by the Investigator as being related to an IMP qualify as adverse drug reactions (ADRs).

Appendix 4 provides a comprehensive list of events that are anticipated to occur in the targeted study entry population of subjects with AI when disease treatment is not optimum.

During the course of the trial, if aggregate analyses indicate that the events are occurring more frequently than anticipated, the Sponsor will notify the IDMC and/or regulatory authorities expeditiously as appropriate.

12.6 Assessment of Adverse Event Expectedness

An AE is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The concept of expectedness does not refer to what may occur in the course of the treated disease such as in the case of disease progression and /or lack of drug effect.

12.7 Serious Adverse Event Definitions

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is life-threatening. Life-threatening, in the definition of serious, refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered serious when, based upon appropriate medical judgment, they may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Similar information to that collected for SAEs will be collected if the application of sick day rules and the occurrence of adrenal crisis is seen. However, the event only needs to be reported as an SAE if they meet the criteria detailed above).

12.8 Serious Adverse Event Reporting

As with all AEs, the Investigator is responsible for the collection of SAE data. All SAEs should be recorded in the specific SAE Case Report Form.

In general, if events as listed in Appendix 4 occur and are considered serious, they will not be reported to regulatory authorities in an expedited safety report since causality will likely be due to the underlying medical condition, rather than to Infacort®.

Any SAE that occurs between administration of the last dose of Infacort® until 7 days after the dose of Infacort® must be reported promptly to the Sponsor or designee not later than 24 hours after the study site becomes aware of its occurrence, using the SAE form provided. Contact details are provided in Appendix 5.

All SAEs should be monitored until they are resolved or stabilised. Any SAEs experienced after this 7-day period should only be reported to the Sponsor if the Investigator suspects a causal relationship to Infacort®. The initial report shall be promptly followed by detailed, written reports using the SAE report form provided. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the subject. The Investigator shall supply the Sponsor and the IEC with any additional requested information.

The report must be made by telephone, facsimile, or email to the Sponsor/designee. An initial report by telephone must be followed up within 24 hours by a faxed or emailed SAE form.

The SAE form requires the following information (at a minimum):

- Subject ID (case number, gender)
- Trial number
- Study therapy
- Concomitant medication (including dose, route, form, regime, start date, if available)
- Nature of SAE (overall diagnosis where available or alternatively signs and symptoms)
- Severity of SAE
- Date and time of occurrence
- Any associated factors (concomitant disease or medication)
- Proposed relationship to study therapy
- Outcome
- Identification of the reporter
- Action in relation to study (withdrawn, suspended, none).

The Investigator or Sub-investigators are required to sign the form and fax or email it to the Sponsor/designee within 24 hours of awareness of the event, even if the required information is incomplete or if the Investigator is waiting for laboratory or diagnostic reports. The original copy of the SAE Report Form and the fax confirmation sheet or sent email (printed out) must be kept with the CRF documentation at the study site.

Investigators may be asked for additional information for any report of an SAE. An SAE form indicated as a follow-up report with attached documents (if necessary) should be forwarded to the Sponsor/designee as soon as the additional information is available.

The Sponsor should submit to the regulatory authorities and IECs all safety updates and periodic reports, as required by applicable regulatory requirements.

12.9 Serious Adverse Event Expedited Reporting

The Sponsor or designee should expedite the reporting to the appropriate regulatory authorities and IECs of all ADRs that are both suspected unexpected serious adverse reactions (SUSARs). Such expedited reports should comply with the applicable regulatory and IEC requirements.

12.9.1 Standards for Expedited Reporting

For each SAE, the Investigator and Sponsor (or designee) will independently assess whether there is a reasonable possibility that the event may have been caused by the IMP (“drug-related”). If the SAE is assessed to be both drug-related and unexpected, the Sponsor or designee will report it to the appropriate regulatory authorities and notify Investigators as required by applicable local regulations. The Sponsor or designee will report SAEs to the German Regulatory Authority (BfArM). SUSARs are required to be reported to BfArM and Eudravigilance within 7 calendar days for life-threatening events and those resulting in death, or 15 calendar days for all others. These timeframes begin with the first notification of the SUSAR to the Sponsor/designee.

SAEs will be reported by the Investigator or designee to the IEC within 7 days for life-threatening events and within 15 days for other events.

12.9.2 Expedited Reporting Guideline for Other Observations

Other safety issues that might be considered for expedited reporting when they could materially alter the current benefit-risk assessment of the IMP (sufficient to consider changes in the administration or in the overall conduct of the trial) include, for example:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important
- Post-study SUSARs that occur after the subject has completed a clinical trial and are reported by the Investigator to the Sponsor
- New event relating to the conduct of the trial or the development of the IMP likely to affect the safety of the subjects, such as an SAE that could be associated with the trial procedures and which could modify the conduct of the trial

12.10 Sponsor’s Responsibilities

The Sponsor is responsible for the ongoing safety evaluation of the IMP by the IDMC and a medically qualified person. The Sponsor is also responsible for ensuring that expedited reports are made to the regulatory authorities and all applicable Investigators of all ADRs that are both serious and unexpected, of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority’s authorisation to continue the trial.

Such expedited reports should comply with the applicable regulatory requirements. The Sponsor should submit to the regulatory authority all safety updates and periodic reports, as required by applicable regulatory requirements.

The Sponsor is responsible for arranging structures and written standard operating procedures (SOPs) to ensure that the necessary quality standards are observed in every step of the case documentation, data collection, validation, evaluation, archiving and reporting.

A case number will be assigned by the pharmacovigilance provider for use in all future correspondence regarding the event and the case number will be forwarded to Diurnal Ltd within 1 working day.

12.11 Independent Data Monitoring Committee

In this study an IDMC has been established to monitor subject's safety. The responsibilities of the IDMC include the following:

- Review the study protocol, Investigator's Brochure and plans for data safety and monitoring
- Review the safety data on an ongoing basis for any emerging safety issues
- Review the annual analysis of safety and biochemical disease control for any issues
- Consider any other relevant information that may have an impact on the safety of the subjects of the study
- Protect the safety of the study subjects
- Make recommendations to the Sponsor concerning continuation, termination, or other modifications to the study based on the observations of the safety in the study.

The details of composition, responsibilities, data to be reviewed and frequency for reviews are laid down in the charter for this IDMC, which will be provided as a separate document.

SAEs will be forwarded immediately to the IDMC for review. All other AE data will be reported on a regular basis.

12.12 Procedures for Reporting Pregnancy Exposure and Birth Events

Not relevant in this study.

13 Statistical Considerations

Analysis of the data will be under the direction of Diurnal Ltd personnel. Full details of procedures for the statistical analysis will be documented in the Statistical Analysis Plan (SAP).

Interim data analyses are expected to be required for regulatory review as part of any marketing authorisation applications.

After the completion of the study and when all data have been checked for plausibility, corrected to the extent possible and all coding and assessments have been completed, the database will be locked.

13.1 General considerations

Only descriptive statistical methods will be used for the statistical evaluation of this study (this includes CIs). All recorded and derived variables will be presented using standard procedures depending on the underlying distribution: for continuous data, sample size, mean, standard deviation (SD), minimum, median and maximum; for categorical data, sample size, absolute and relative frequency. The behaviour over time of continuous and categorical data will be analysed by presenting summary statistics for the actual values and change from baseline at each visit, if appropriate. No missing data will be replaced for any secondary variable.

13.2 Biochemical Disease Control and Safety Variables

13.2.1 Primary Variable

SAEs and AEs observed throughout the study.

13.2.2 Secondary Variables

SDS for height and weight, cortisol (all subjects) and adrenal androgen levels (17-OHP, A4, testosterone) in CAH subjects only.

13.3 Methods of Analysis

13.3.1 Analysis Populations

Protocol Violations/Deviations

Any protocol violations/deviations will be reviewed and classified as either ‘minor’ (unlikely to appreciably affect the trial outcomes) or ‘major’ (likely to affect outcomes).

Safety Population

The Safety Population will include all subjects who receive one complete or a partial dose of Infacort®. All analyses will be conducted on the Safety Population.

13.3.2 Statistical Evaluation

13.3.2.1 Adverse events

The analysis of AE data will be described in detail in the SAP. All information obtained on AEs will be displayed in listings and subject, including demographic information. The number and percentage of subjects with AEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT). A subject with multiple AEs within a SOC or PT is only counted once towards the total of this SOC or PT.

Further AEs tables, for example by severity, relationship or outcome, will be presented if the number of events make such table useful information.

Analyses and detailed listings of AEs with particular relevance for the formulation (such as choking, vomiting related to dosing etc.) and to AI (sick days, adrenal crisis etc.) will be presented separately.

13.3.2.2 Growth Velocity

SDS for height and weight will be calculated for each subject using an age- and gender-matched German healthy reference cohort. Details will be described in the SAP.

13.3.2.3 Adrenal Cortisol and Androgen Levels

Blood concentrations data taken from dried blood spot samples (cortisol and androgen levels) will be listed and presented in summary statistics (sample size, arithmetic mean, geometric mean, SD, coefficient of variation (CV), minimum, median and maximum) for each cohort and overall. Time-concentration curves will be presented for individual subjects and also for each cohort and the subject group as a whole. These data may be merged with that collected in the Infacort 003 study for population PK analyses.

13.3.3 Analysis of the Conduct of the Study

Data concerning the conduct of the study (e.g. inclusion/exclusion criteria, subject disposition/withdrawals, and protocol violations) will be listed by subject for the safety population. Details will be described in the SAP.

13.3.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be listed and summarised for the safety population. BMI and BSA will be derived from the recorded height and weight. Medical history and current medical status and previous and concomitant medication/treatment will be listed by subject, including an index if the onset was before or after Infacort® intake. Frequency tables (n and %) for the coded events will only be provided if the number of events make such a table useful information.

Drug administration data will be listed by cohort and subject.

13.3.5 Tanner Development Stage

A frequency table for the stages at each visit and shift tables from the initial visit will be presented.

13.3.6 Sick Days

The number of days will be presented by visit using frequency tables and, if useful, the number of subjects with no sick days, up to 7 sick days, and greater than 7 days will also be presented. Complete details will be provided in the SAP.

13.3.7 Safety Analysis

All vital signs data will be listed by subject, and visit/time and if ranges are available abnormalities (and clinically significant changes) will be flagged. Summary statistics will be provided overall and by visit/time. All reasons for discontinuation will be listed by subject. All physical examination data will be listed by subject. Shift tables comparing screening/baseline ratings with the ratings at end of study will be presented for each category.

Electrolytes, renin, haematocrit, and any additional cortisol data values will be listed and presented in summary statistics (sample size, arithmetic mean, geometric mean, SD, CV, minimum, median and maximum) for each cohort and overall. Time-concentration curves will be presented for individual subjects and also for each cohort and the subject group as a whole.

These data may be merged with that collected in the Infacort 003 study for population PK analyses.

13.3.8 End of Study Information

All end of study data will be listed and a frequency table about completion and reason for termination will be provided, if useful.

13.3.9 Miscellaneous

All statistical analysis will be performed using the software package SAS version 9.1 or higher (SAS Institute Inc., Cary, NC 27513, USA). Missing data will be treated as missing and no attempts will be made to impute values for missing data. Any statistical analyses not described in the protocol or the SAP will be documented in the study report.

The versions of the following international dictionaries current at the time of study conduct will be used for medical coding:

- Diagnoses: Medical Dictionary for Regulatory Activities (MedDRA)
- Medications: World Health Organisation (WHO) Drug Dictionary including ATC classification
- Adverse events: MedDRA

13.4 Power and Sample Size Considerations

No formal sample size calculation is provided for this study since only subjects who have previously been treated in study Infacort 003 can enter this study. Hence the maximum number of subjects in this study is 24.

13.5 Ongoing Reviews and Annual Reports

All emerging safety data will be assessed for any signal of safety problems on an ongoing basis. An analysis of safety and biochemical disease control (overseen by the IDMC) will be undertaken on a yearly basis (this may be abbreviated in the early years when there is insufficient data to undertake a full analysis). Details of the data to be provided at the IDMC review meetings will be provided in the SAP.

14 Responsibilities

14.1 Investigator Responsibilities

By signing the protocol, the Investigators agree to:

1. Conduct the study in accordance with the protocol and make changes only after agreement from the Sponsor, except in cases to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Inform any subjects enrolled in the study that the drug is being used for investigational purposes.
4. Ensure that the requirements relating to obtaining informed consent and IEC review and approval are met.

5. Report to the Sponsor any AEs/SAEs that occur during the course of the study, in accordance with International Conference on Harmonisation (ICH) guidelines.
6. Have read and understood the Investigator Brochure, including potential risks and side-effects of the drug.
7. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
8. Maintain adequate and accurate records and to make those records available for inspection with the Sponsor, their designated representative, or any agency authorised by law.
9. Ensure that an IEC will be responsible for initial and continuing review and approval of the clinical study.
10. Report promptly to the IEC and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and safety reports).
11. Not make any changes in the research study without approval, except when necessary to eliminate hazards to the subjects.
12. Comply with all other requirements regarding the obligations of the clinical Investigators and all other pertinent requirements.

Protocol adherence

Investigators confirm they will apply due diligence to avoid protocol deviations. If the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Diurnal and approved by the IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report (CSR).

Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Diurnal, Health Authorities where required, and the IEC. Only amendments that are required for subject safety may be implemented prior to IEC approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Diurnal should be notified of this action and the IEC at the study site should be informed within 10 working days.

14.2 Ethical Conduct of the Study

The study will be conducted according to ICH Good Clinical Practice (GCP), the Declaration of Helsinki (1996), and IEC and BfArM requirements.

14.3 Independent Ethics Committee Approval

The study protocol, subject information and consent form will be presented to the relevant IECs. The study will only start at a study site after ethics approval has been granted. The IECs will immediately be informed (by the Sponsor) of all changes to the protocol (according to GCP-V § 10) and of all events that could affect a subject's safety. The IECs will also be informed of all suspected SUSARs and of regular or premature termination of the study.

The Investigators have to register with the IECs (together with proof of qualification) before they enrol any subjects.

14.4 Informed Consent

The principles of informed consent in the Declaration of Helsinki (1996), in the current requirements of GCP published by ICH and local regulation, whichever affords the greater subject protection, will be implemented before any protocol-specified procedures or interventions are carried out.

Before enrolment every subject (parent/carer) will receive full oral and written information about the nature, purpose, expected advantages and possible risks of the trial. The parent/carer will agree to participation in the trial by signing the informed consent form. They will be 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 shall be documented on the consent form by the dated signature of the subject's parent/carer and the Investigator/treating doctor.

Design of the forms and language will be adjusted to the study site's needs. The final versions of subject information and consent will be presented to the IECs. Both the subject information and the subject consent form are prepared in duplicate. One of each form will be retained by the Investigator, a duplicate will be given to the subject.

All information sheets and consent forms will be provided in German.

14.5 Case Report Forms

CRFs will be provided for each subject. Subjects will not be identified by name or initials on any study documents (or copies) retrieved from the site (for subject confidentiality). The subject identification number entered upon study entry shall identify each subject.

All data on the CRF must be legibly recorded in black or blue ink. Corrections are to be made by striking through the incorrect information and writing the revision alongside. All corrections must be initialled and dated. All relevant information recorded in the diary cards must be transcribed into the CRF by the Investigator or designee. The Investigator must review the CRFs for completeness and accuracy and must sign and date the appropriate CRF pages as indicated. The Investigator will retain full responsibility for the accuracy and authenticity of all data entered on the CRFs. CRFs will be reviewed at the study site during regularly scheduled visits by study monitors.

A copy of the CRF with all related corrections and queries should be kept at the study site; the original copy (and any other copies) will be collected by the local monitor.

All data collected in the CRF will be double entered into a validated computerised clinical data management system.

14.6 Site Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Diurnal representative will review the protocol and CRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to GCP, the progress of enrolment, and to ensure that the IMP is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The Investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject). Note: see Appendix 6 for handling of documents at remote sites.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of AEs and SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

14.7 Source Data Verification

The information in original documents and records (e. g. patient files, laboratory notes, diary cards etc.) are defined as source data and will be reviewed by the monitor for source data verification (SDV). All data that will be recorded directly in the CRF without prior written or electronic record will be described in the protocol and considered to be source data. SDV ensures accuracy and credibility of the data obtained. During monitoring visits reported data are reviewed with regard to being accurate, complete and verifiable from source documents (e.g. subject files, recordings from automated instruments, laboratory notes).

14.8 Subject Confidentiality/Data Protection

All data forwarded to the Sponsor or designees will be identified only by a subject number. The Investigator agrees that representatives of the Sponsor, its designee, representatives of the relevant IECs, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this trial (including, but not limited to, laboratory test result reports, admission/discharge summaries for hospital admissions occurring during a subject's trial participation and autopsy reports for deaths occurring during the trial).

The subjects' data will be saved in a pseudonymous form. All regulative requirements applying to data protection will be met. Re-identification of a subject's name will be possible from the

subject identification log, which is kept in a locked research office at the trial site where access is only possible by the Principal Investigator or persons authorised by the Principal Investigator.

Subjects (parent/carer) will be informed that their disease-related data will be saved for scientific purpose (publication, etc.) using a pseudonym. Consenting subjects (parent/carer) have got the right to be informed about the data recorded. Subjects (parent/carer) will also be informed that their pseudonymised data will be forwarded to BfArM and to the IECs responsible, in accordance with legal notification obligation for drug safety. Subjects (parent/carer) who disagree with this process of data transfer will not be allowed to participate in this study.

14.9 Data Management

All data collected in the CRF will be transferred via double-data-entry method to a validated computerised clinical data management system. The final data management process contains the plausibility, consistency and range checks of the entered data. In case of faulty or missing data the data manager will generate data management queries and send them to the site. Implausible or missing data will be corrected or added after consulting the Investigator. Documentation for these corrections will be stored with the CRFs. The data correction in the database will be performed with scripts in SAS or directly in the study database.

After all data management steps are finished, the database will be locked and will be available for the statistical analysis.

14.10 Drug Accountability

The monitor will perform drug accountability checks. The medication provided for this study is for use only as directed in the protocol. It is the Investigator/institution's responsibility to establish a system for handling study treatments, including IMPs, so as to ensure that:

- Deliveries of such products from Diurnal Ltd are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to study subjects in accordance with the protocol
- Any unused products are either returned for destruction or destroyed on site in liaison with the Sponsor.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed and the quantity and date of dispensing. This record is in addition to any drug accountability information recorded on the CRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigational pharmacist, and copies retained in the Investigator Site File.

All unused medication should be either returned for destruction or destroyed by the Charité Pharmacy following appropriate drug accountability procedures and authorisation from the Sponsor.

14.11 Inspections

The Sponsor or Sponsor representative or external regulatory agency may at any time during or after completion of the study conduct a GCP audit. Notice will be given to the site in advance of a planned GCP audit.

14.12 Sponsor Responsibilities

14.12.1 Indemnity and Compensation

For participating subjects, an insurance () is in force. The insurance is provided by , and will cover incidents for the study duration (from 1st Feb 2015 for 30 months but will be extended if necessary). The insurance is limited to a maximum of 500,000 Euros per subject.

Terms for the provision of indemnity and for the provision and maintenance of insurance will be documented in contracts between Diurnal Ltd and the relevant parties.

14.12.2 Subject Confidentiality

The Sponsor's staff or any designees affirm and uphold the subject's privacy/confidentiality. Throughout this trial, all data forwarded to the Sponsor or designees will be identified only by a subject number.

14.13 Publication Policy

The study results will be published irrespective of the study outcome. No confidential subject information will be published.

The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. Publication of the results will not include confidential information without the permission of the Sponsor.

The Sponsor may announce quality assured summary data in order to comply with Financial Regulatory Authorities, whilst ensuring that release of such data will not compromise the Investigator's ability to publish the data in appropriate scientific forums. No announcements will be made prior to the publication of the Principal Investigator's manuscript, unless reviewed and authorised by the Principal Investigator.

14.14 Clinical Study Report

The results of the study will be presented in an integrated CSR according to GCP and ICH-E3 guidance.

14.15 Data Retention and Availability

The Investigator is required to maintain all study documentation, including regulatory documents, copies of CRFs, signed informed consent forms, and records for the receipt and disposition of study medications, for a period of 2 years following approval date of the last Marketing Authorisation Application for the drug, or until 15 years after completion of the study, whichever is later.

During and after the study, the Investigator must make study data accessible to the Sponsor, IECs and appropriate regulatory authorities. A file for each subject must be maintained that includes the signed informed consent form and copies of all source documentation related to that subject. The Investigator must ensure the availability of source documents from which the information on the CRF was derived.

14.16 Study Termination

The study may be terminated at any time at the request of the Sponsor, the Investigator, the IECs or Regulatory Authorities or by mutual agreement. Conditions that may warrant early termination include, but are not limited to, insufficient adherence to the protocol requirement, the discovery of a significant, unexpected and unacceptable risk to the subjects, attainment of study objectives, or at the discretion of the Sponsor. Procedures for terminating the study will be agreed upon by both the Sponsor and the Investigator.

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Appendix 1 – Blood Spot Analysis

Where possible the blood spot sample should be taken in the morning. Blood spots will be collected from either venous or capillary samples using the following procedure:

- All samples will be collected in aseptic conditions (i.e. the area to be sampled will be wiped with an antiseptic wipe).
- Whatman® Protein Saver 903® paper will be used to collect all the samples.
- If using capillary sampling, the lateral finger pad will be pricked with a sterile lance.
- The first drop will be used to soak the 5 circles on the blood spot card, with the blood being put against one side of each circle and allowed to soak across. Each blood spot is approximately 75-80 µL, giving a total blood volume of 375 µL per card.
- The blood spots will be dried for 2-4 hours at room temperature (kept away from direct sun and heat).
- The dried blood spots will be sent to the laboratory at Charité-Universitätsmedizin Berlin on the same day as the samples are taken.
- The dried blood spots must be transported and stored at room temperature.
- The dried blood spots will be stored for up to 15 years.

The following analytes will be analysed from the blood spots:

17a-hydroxyprogesterone
Deoxycorticosterone
Androstenedione
Testosterone
Dihydrotestosterone
Cortisol
11-Deoxycortisol
21-Deoxycortisol
Corticosterone
17-Hydroxypregnenolone
Pregnenolone
Dihydro-Epi-Androstendion
Progesterone
Aldosterone
Cortisone

Appendix 2 – Tanner Development Stages

Pubic hair

PH1	No pubic hair
PH2	Sparse, pigmented hair mainly on labia, at base of penis
PH3	Coarser and darker hair spread over mons pubis
PH4	Adult type hair but not spreading to medial surface of the thighs
PH5	Adult type hair and distribution
PH6	Adult type hair and distribution, spreading along linea alba

Breast

B1	Papilla elevation
B2	Palpable breast buds; areola enlargement
B3	Areola and breast enlargement; no projection of the areolae
B4	Projection of areola and papilla to form secondary mound
B5	Mature with projection of papilla only

Genitalia

G1	Penis size prepubertal, testes <4mL volume, long axis <2.5 cm
G2	Early penile and scrotum growth, testes 4-8 mL volume, length 2.5 to 3.3 cm
G3	Increase in penile length and width, testes 10-15 mL volume, length 3.4 to 4.0 cm
G4	Increase in penile length and width, scrotum pigmenting, testes 15-20 mL volume, length 4.1 to 4.5 cm
G5	Adult size and shape penis, testes >20 mL volume, length >4.5 cm

Appendix 3 – Sick Day Rules

Each site should follow their own sick day rules, or if these are not available then the following rules should be used:

Emergency situation measures to be taken by the parent/carer

Intercurrent illness with:

Fever

>38°C - double oral hydrocortisone dose as long as body temperature continues to be elevated

>39°C - triple oral hydrocortisone dose as long as body temperature continues to be elevated

>40°C - increase oral hydrocortisone dose 5-fold as long as body temperature continues to be elevated

Vomiting, diarrhoea

Triple the oral hydrocortisone dose (starting immediately). In case of repeated vomiting, administer prednisone (100 mg) as a suppository. Patient should be seen by a physician without delay. If the clinical condition worsens rapidly, call an ambulance (112) or take the child to the local emergency room.

Emergency measures by trained medical personnel

Shock, severe trauma, coma, emergency surgery:

give i.v. bolus of hydrocortisone:

- 25 mg at age < 6 months
- 50 mg at age 6 months to 6 years
- 100 mg at age > 6 years

Alternatively, any other glucocorticoid available can be given at an equivalent dose, e. g. methylprednisolone at 5 mg, 10 mg, and 20 mg, respectively.

This should be followed by a continuous infusion of hydrocortisone 150 mg/m²/24 hours until the subjects condition has stabilised.

Initial basic solution for parenteral fluid therapy (all age groups including infants and young children): mix 450 mL 0.9% NaCL + 50 mL 40% (or 50%) glucose (adjust total volume and infusion rate to the results of continuous monitoring of fluid and electrolyte balance). In general, at parentally administered high hydrocortisone doses there is no need for additional mineralocorticoids.

Appendix 4 – Anticipated Events in the Target Population

A list of anticipated events in this group of subjects is detailed below:

- chronic fatigue
- anorexia
- asthenia
- nausea
- vomiting
- loss of appetite
- weight loss
- recurring abdominal pain
- weakness and a lack of energy
- increased skin pigmentation
- salt craving
- hypoglycaemia
- hypotension
- orthostatic changes in blood pressure and heart rate (pulse)
- altered mental status

Appendix 5 – Contact Details for Serious Adverse Events

All SAEs should be reported to [REDACTED]:

[REDACTED]
[REDACTED]
[REDACTED]

Appendix 6 – Remote Site Guidelines

Background

Subjects participating in Infacort 004 were previously enrolled in Infacort 003. In the third cohort of Infacort 003 in which neonates (<28 days) were recruited, some subjects were identified in centres outside the Charité Universitätsmedizin Berlin. Two of these subjects were enrolled into Infacort 004 and visited the Charité Universitätsmedizin Berlin for the purpose of study visits. However, due to the travelling time and consequent associated practicalities, one of these subjects, although still having their care transferred to Charité Universitätsmedizin Berlin for the remainder of the study, will have their visits conducted by the Charité staff at the subject's local hospital. Thus for the purposes of the study procedures, this subject (and any further subjects enrolled into the study on this basis) will be considered to be under the care of Charité Universitätsmedizin Berlin.

Establishment of remote sites

The Charité Investigator will contact the local physician and provide study information, to include required supply of study-specific medical supplies and equipment availability. The Charité Investigator will provide a treatment agreement for execution, to include agreement on the use of the local site's treatment rooms, study-specific medical supplies and equipment, and laboratory facilities.

The local physician will send a request for consultation treatment to the Charité Investigator.

Subject recruitment

The local physician will remind the parents/carers about the opportunity for their child to enrol into the study following completion of participation in study Infacort 003. Where parents/carers confirm their interest in participation of their child in the study they will give consent for issue of their contact details to the Charité Investigator by their local physician. The Charité Investigator will contact the parents/carers informing them about the study and confirming continuing interest in participation of their child. The Charité Investigator will provide the parents/carers with the Information Sheet and Consent Form to provide adequate time for them to consider participation of their child. The Charité Investigator will provide the parents/carers with the practical details of their participation in the study at the remote site such as the dates for study participation. The Charité Investigator will confirm each of their visits to the remote site with the local physician.

IMP

The Charité Investigator will issue a prescription for Infacort® to the Charité Pharmacy either calculated from that dispensed at the previous visit, or from information provided by the local physician, and with the necessary overage to allow for both repeated dosing in the case of incomplete administration and any increases in dose in the event of the necessity for implementation of sick day rules. The Charité Pharmacy will dispense the prescription for collection and transport either by courier to the Charité Investigator at the remote site or by the Charité Investigator him-/herself. Temperature monitoring during transport to the remote site in either event, included with the IMP shipment, will be downloaded by either the courier or the Charité Investigator and provided to the Sponsor to confirm that the transportation conditions were acceptable prior to administration and supply of the IMP to the subject. All unused medication and empty (used) Infacort® capsules that are returned by the subject's parents/carers at each visit will be sent by the Charité Investigator to the Charité Pharmacy in Berlin for the purpose of IMP accountability verification.

Completion of study procedures at the remote site

The Charité Investigator will arrive at the local site in advance of the subject's arrival. The local physician will arrange for a formal handover of their patient to the care of the Charité Investigator for the duration of each study visit. The Charité Investigator will perform the visit study procedures, including blood sampling, in accordance with the study protocol. The additional blood samples for routine clinical care can be taken simultaneously by the local physician.

The Charité Investigator will train the parents/carers in how to administer the study medication at the initial visit since parents/carers will be administering the Infacort® to the subjects at home. Parents/carers will also be given an instruction sheet to take home with them for reference by the Charité Investigator, which will include written instructions on the dose to be taken. They will also be instructed in how to complete the diary card, and they will be asked to bring this along to all visits.

At Visit 1, the Charité Investigator will attend with an emergency case which will include the standard contents as required by the Charité Universitätsmedizin Berlin.

After each study visit the Charité Investigator will arrange for a formal handover of the subject to the care of the local physician.

Study sampling

All study samples will be taken in accordance with the study protocol. The collected blood spots will be transferred under ambient conditions to Charité Universitätsmedizin Berlin by the Investigator for analysis of steroid metabolites.

Electrolytes, renin, haematocrit, and any additional cortisol data will also be collected where collected routinely by the local laboratory as part of the routine clinical care (normally once a year). The results of all these analyses will be included in the database.

Study Data Management

All study-specific documentation will remain with the Charité Investigator and be transferred to Charité Universitätsmedizin Berlin. Redacted results reports following analysis of electrolytes, renin, haematocrit, and any additional cortisol data (where collected for routine care) will be provided to the Charité Investigator when available for inclusion in the database. Subject selection is to be confirmed by the Charité Investigator by checking through all inclusion/exclusion criteria at the initial visit. A record of this check (e.g. inclusion/exclusion checklist) will be stored with the source documentation at the remote site. Any change to medical history and current disorders, and all concomitant medications since conclusion of participation in Infacort 003 will be confirmed by the Charité Investigator through reference to the subject's medical records and included in the CRF by the Charité Investigator. Copies of medical records entries will not leave the remote site. The Charité Investigator will record all information relevant to the subject's participation in the study while at the remote site. One copy will remain in the local notes (subject's medical records) and one will return to Charité Universitätsmedizin Berlin as the sole source data.

The study monitor will monitor the CRFs and diary cards with associated source document verification at Charité Universitätsmedizin Berlin.

Appendix 7 – Protocol Amendment History

Protocol Version 1.0 dated 23 July 2015

Original protocol.

Protocol Version 2.0 dated 15 September 2015

The following clarifications were made to the protocol prior to any subjects being enrolled:

- 1) The early withdrawal criteria of ‘new medical conditions that may impair the safety of the subject’ was expanded to provide the example of any condition that impairs the subject’s ability to swallow, which may preclude oral medication.
- 2) The early withdrawal criteria of ‘decision of the Investigator if he/she considers the subject’s health may be compromised by remaining in the study’ was expanded to clarify that the investigator may consider this if there are more than 3 episodes of sick day rules without reasonable explanation (eg infection, fever, trauma etc), or two or more episodes of Addisonian Crisis without reasonable explanation (eg infection, fever, trauma etc).

Protocol Version 3.0 dated 25 July 2016

The following changes were made to the protocol:

- 1) The Sponsor signatory was changed from [REDACTED]
- 2) The telephone number of [REDACTED] was added in Appendix 5 and the international dialing code added to the fax number.
- 3) Interim data analyses are 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.
- 4) In addition to the Infacort® granules being administered directly onto the top, and towards the back, of the child’s tongue, the granules can now also be mixed with yoghurt, fruit purees (e.g. apple sauce) or fruit mousses immediately before being administered to the child. The granules can 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.
- 5) 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 changed to specify generic names.
- 6) 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.
- 7) Section 8 stated that, if agreeable, subjects from remote sites could be cared for at Charité-Universitätsmedizin Berlin, CVK, for the purposes of the study. For clarity this statement was added to the synopsis as well.

- 8) Blood spot samples will be taken every month for the first 2 months of the study, then every 6 months unless required after 3 months. The synopsis text was updated for clarification.
- 9) 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.
- 10) The address for [REDACTED] at [REDACTED] was updated.
- 11) The Infacort® capsules will now be supplied in both blister packs and bottles. Therefore Section 10.2.2 (Packaging and Labelling) was updated.

Protocol Version 4.0 dated 20 July 2017

The following changes were made to the protocol:

- 1) The Sponsor signatory was changed from [REDACTED]
- 2) Confirmed in Section 12.3.6 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.
- 3) In some cases, whilst the subject is cared for by Charité-Universitätsmedizin Berlin for the purposes of the study, it may be necessary of the Investigator at Charité-Universitätsmedizin Berlin to visit the subject at their local hospital. A detailed procedure for this scenario has been added as Appendix 6.
- 4) In line with the proposed labelling for Infacort®, 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'.
- 5) The protocol currently states that subjects can continue to be treated in this study until they meet the study withdrawal criteria, Infacort® is granted a marketing authorisation (and so is available commercially), Infacort® is refused a marketing authorisation, or the Sponsor decides to discontinue the study. A footnote has been 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.
- 6) Published data are now available on the study conducted at Berlin on the lack of formal quality control of crushed tablets so the information has been updated in Section 5.4 (Rationale) and the formal reference added.
- 7) Added to Section 8.14 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.

- 8) Testing of hydrocortisonacetat in the blood spot analyses (Appendix 1) was removed since this is no longer analysed by the laboratory.
- 9) After discussion with the Investigators, it was discovered that no mean and SD for the age- and gender-matched German reference population was available. So it was decided that the secondary endpoint of growth velocity would not be used, but instead the SDS 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.