Statistical Analysis Plan
for

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
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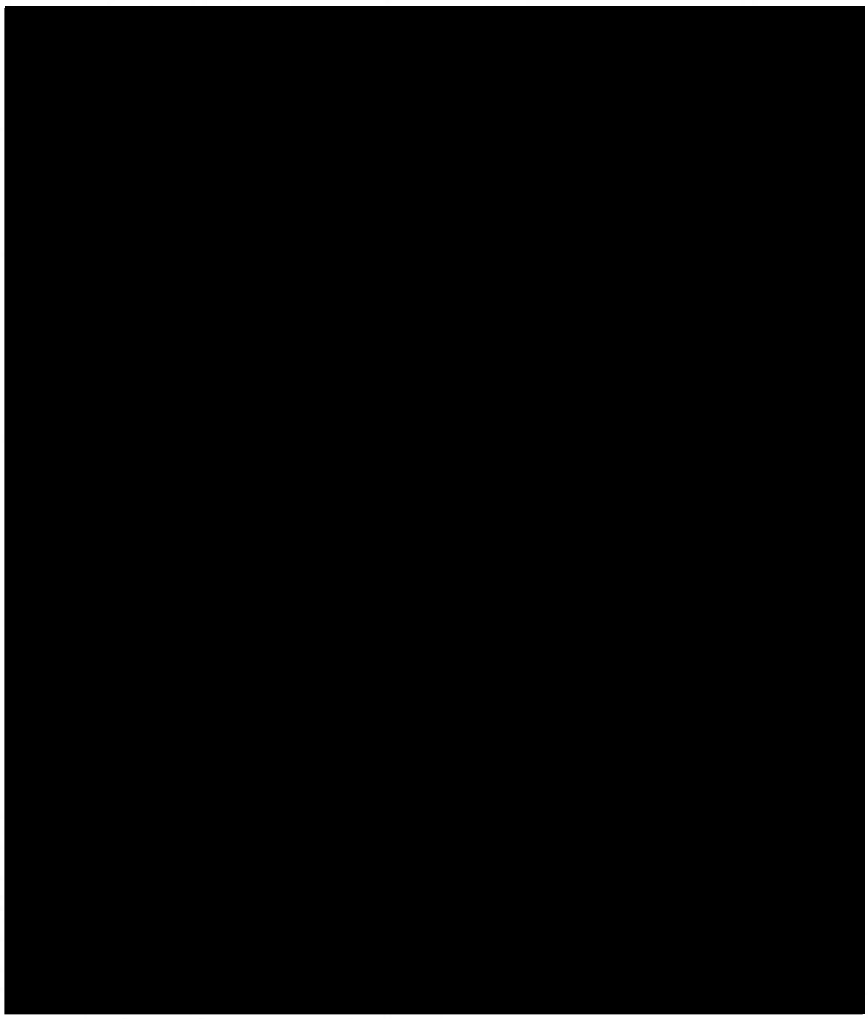

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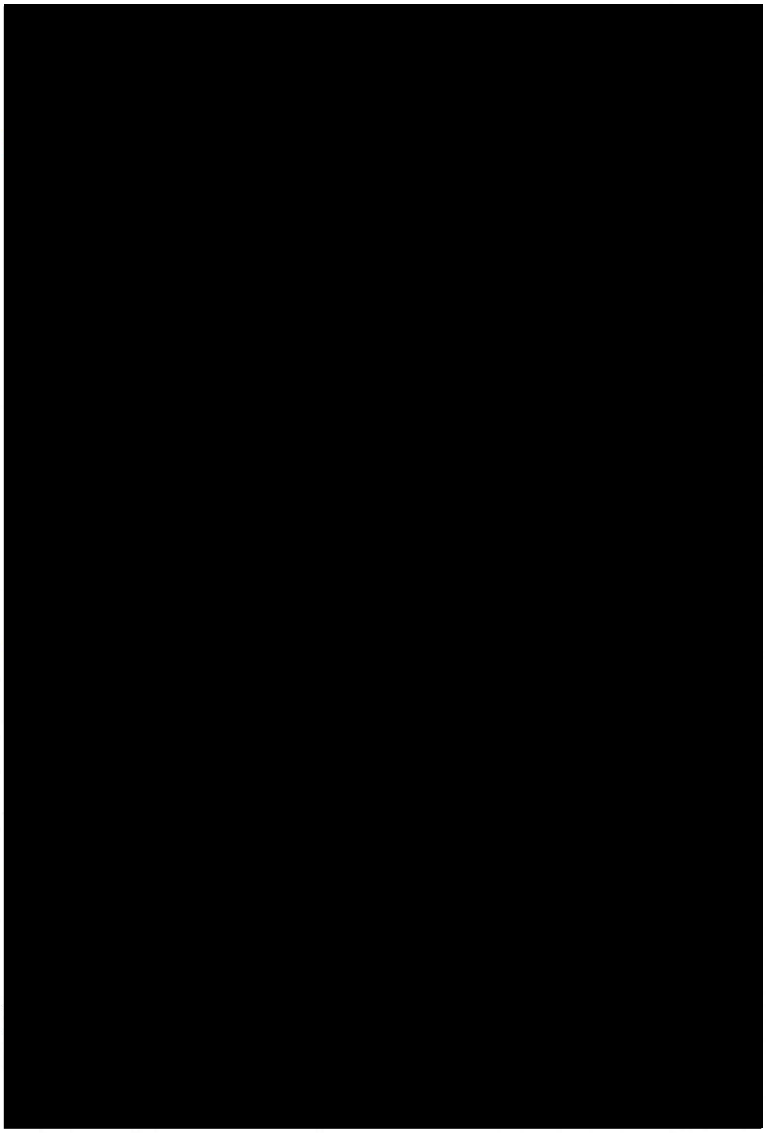

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GLOSSARY OF ABBREVIATION

17-OHP	17-hydroxyprogesterone
A4	Androstenedione
AE	Adverse Event
AI	Adrenal Insufficiency
ATC	Anatomical Therapeutical Chemical
ATCH	Adrenocorticotropic Hormone
BMI	Body Mass Index
BSA	Body Surface Area
BS	Body System
CAH	Congenital Adrenal Hyperplasia
CRF	Case Report Form
CRO	Contract Research Organisation
DM	Data Management
DMP	Data Management Plan
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
GCP	Good Clinical Practice
GV	Growth Velocity
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PR	Pulse Rate
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDS	Standard Deviation Score
SEM	Standard Error of the Mean
SOC	System Organ Class
SOP	Standard Operative Procedure
WHO-DRL	World Health Organisation Drug Reference List

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses and data presentations to be performed on this Phase III, open-label, single-group, non-randomised, observational study of the safety and biochemical disease control of Infacort® in neonates, infants and children with adrenal insufficiency (AI) who have completed study Infacort 003.
This analysis plan is developed based on ICH E3 and E9 Guidelines and in reference to the following documents:

- Protocol Infacort 004, Version 2.0 dated September 15, 2015
- Protocol Infacort 004, Version 3.0 dated July 25, 2016
- Case Record Form, Version 1.0 (final) dated December 15, 2015

Remark: Date of birth, gender, race/ethnicity, and medical history will not be collected in the CRF of Infacort 004. This data will be transferred from the database of the Infacort 003 study.

It should be mentioned that a summary of all safety data will be forwarded to an Independent Data Monitoring Committee (IDMC) at regular time intervals for a detailed safety review. In addition, on request of the European Medical Agency a safety interim analysis will be performed 6 months after the first visit of the first subject in this study, in order to support a planned Marketing Authorisation Application intended for submission Q4/2016. Thereafter additional safety interim analyses for review by the IDMC will be performed on a yearly basis. The analysis may be abbreviated in the early years when there is insufficient data to undertake a full analysis. The IDMC will indicate to the Sponsor and the Principal Investigator their recommendation on continuing and/or modification of the study, or of immediate termination of the study. Details of these procedures will be defined in a separate document.

Any significant changes from the analysis methodology defined in the protocol/CRF or protocol amendments agreed after the approval of this SAP may require changes to this SAP, see section 5.13.

2. STUDY OVERVIEW

2.1 Study Objectives and Hypotheses

The primary objective of this study is to gather data on the long-term safety of Infacort® in neonates, infants and children completing study Infacort 003.

The secondary objective of this study is to gather data on the effects of Infacort®.

2.2 Study Design

This protocol is based on a Paediatric Investigation Plan (PIP) that has been agreed by the EMA (EMEA-001283-PIP01-12).
This is a phase III, open label, single group, non-randomised, observational study of Infacort® in neonates, infants and children with AI who have completed the study Infacort 003. The study will be conducted in up to 24 subjects, requiring replacement therapy for AI due to either CAH, primary adrenal failure or hypopituitarism. All subjects who have satisfactorily completed study Infacort 003 will be offered the opportunity to take part in this Infacort 004 study. The study protocol was 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.
The primary site will be Charité-Universitätsmedizin Berlin, CVK. However, some subjects participating in Infacort 003 may have been enrolled at remote sites, see Infacort 003 study protocol for details. Should their parents/carers consent to participation in Infacort 004, additional study centres may be involved (or, if agreeable, the subjects may be cared for at Charité-Universitätsmedizin Berlin, CVK, for the purposes of the study).

Details of the inclusion/exclusion criteria are defined in Sections 9.3 and 9.4 of the study protocol.

All subjects who have satisfactorily completed the study Infacort 003 will be offered the opportunity to participate in study Infacort 004 at or after their final visit of study Infacort 003. 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.
The standardised protocol for follow-up will include the following visits:

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

So, the first visit will be labelled month 0, the second visit month 1, the third visit month 2, the fourth visit month 5, the fifth visit month 8, the sixth visit month 11 and so on until the end of the study, labelled as month 999.
Subjects can continue to be treated in this study until they meet the study withdrawal criteria (see Section 11 of the protocol), Infacort® is granted a marketing authorisation (and so is available commercially, which the Sponsor anticipates will occur within 2 years of initiation of this study), Infacort® is refused a marketing authorisation, or the Sponsor decides to discontinue the study.

The study procedures to be conducted for each subject enrolled into the Infacort 004 study are detailed in **Table 1** (see section 8.1 of the protocol for more details).

Table 1: Schedule of Study Assessments

	Initial Visit	Interim Visits[1]	Final Visit
Visit number/month	**0**	**1,2,5,8,11,14, etc.**	**999**
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.
[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.

2.3 Data and Analysis Quality Control

The Data Management Plan (DMP) will detail the quality assurance and quality control systems to be implemented to assure the quality of the data. Similarly, the quality control of the statistical analysis will follow the standard procedures of the unit performing the statistical analyses.

3. PRIMARY VARIABLES

The primary safety endpoint will be the nature and occurrence of Serious Adverse Events (SAEs) and Adverse Events (AEs) including application of sick day rules and adrenal crises observed throughout the study.

The key secondary endpoints are:
- Growth velocity (linear growth velocity standard deviation score [SDS])
- Cortisol (all subjects) and adrenal androgen levels (17-OHP, A4, testosterone) in CAH subjects only

The safety variables include:
- AEs and SAEs
- Laboratory assessments
- Vital signs including weight and height

4. SAMPLE SIZE JUSTIFICATION

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.

5. MEHODS OF ANALYSIS AND PRESENTATION

5.1 General Principles

The statistical analysis will be performed by a statistical unit, using SAS version 9.1 or later. Any statistical analyses not described in the protocol or in this SAP will be documented in the study report.

All recorded and derived variables will be presented by cohort and overall (and by visit, if appropriate) using appropriate descriptive summary tables (continuous data: sample size, mean, standard deviation (SD), minimum, median, maximum; categorical data: sample size, absolute and relative frequency). Missing data will be treated as missing and no attempts will be made to impute values for missing data. 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.
Specifically, data collected at unscheduled visits will be listed only and will be excluded from summary statistics.

In all summaries, the groups will be displayed in the following order: cohort 1, cohort 2, cohort 3 and overall. All collected information will be listed sorted by cohort and subject number for the safety population. Subjects who didn't receive study medication will be listed separately.
For all parameters, baseline is defined as the last available pre-treatment value (i.e. the last non-missing value available before Infacort® intake).

Only descriptive statistical methods will be used in the analyses of the data. In addition, due to the low number of subjects in this study and depending on the actually collected data some of the below described tables/analyses may not provide useful information. In this case tables/analyses will be omitted.

5.2 Definition of Analysis Populations

The following analysis sets will be used for the statistical analysis:

Screening Population	All subjects who were screened (i.e., gave informed consent)
Safety Population	The Safety Population will include all subjects who receive a complete or a partial dose of Infacort®.

Protocol Violations/Deviations
All protocol violations/deviations will be reviewed and classified as either 'minor' (unlikely to affect trial outcomes) or 'major' (likely to affect the trial outcome).

5.3 Disposition of Subjects

A summary of the subjects' disposition will be created including: number of subjects screened, number of screen failures, number of eligible subjects not treated, number of subjects treated in each cohort and overall, number of subjects who completed the study in each cohort and overall. In addition, a summary of the number and percentage of subjects in the safety population who discontinued the study and their reasons for discontinuation will be presented by cohort and overall.

5.4 Demographic and Baseline Characteristics

Demographic characteristics (age [days], gender and ethnic origin), body measurements (height, weight, Body Mass Index [BMI], Body Surface Area

[BSA] and causes for AI will be summarised by cohort and overall for the safety population.

Age (in days), BMI and BSA will be calculated as:

- Age (in days) will be calculated as the difference in days between date of birth and date of first study drug administration.

- The BMI in kg/m^2 will be calculated using the following formula:

  BMI = W / (H*H)

  where W is weight in kg, and H is height/length in m.

- The Body Surface Area (BSA in m^2) will be calculated using Du Bois's formula

  $$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$$

  where W is weight in kg, and H is height in cm.

All inclusion and exclusion information will be listed only.

5.5 Medical History

Medical History and Concurrent conditions will be coded using MedDRA, version 18.1 or higher.

The number and percentage of subjects with past medical conditions, i.e. not ongoing at baseline, grouped by MedDRA SOC will be displayed by cohort and overall for the safety population. A similar summary will be produced for concurrent medical conditions, i.e. ongoing at baseline.

However, these frequency tables (n and %) will only be provided if the number of events make such a table useful information.

5.6 Physical Examination

The number and percentage of subjects with normal/abnormal physical examination will be displayed over time for each body system as indicated in the CRF and for each cohort and overall in the safety population.

Shift tables comparing baseline (visit 1) ratings with the ratings at the interim visits will be presented for each category by cohort and overall. These shift tables may be omitted if not useful.

The following categories will be examined: skin, ears, nose, throat, lungs, heart, abdomen, back, genital status, basic nervous system and other.

5.7 Protocol Deviations

The number and percentage of subjects for each category of the protocol deviations will be summarised for the safety population.

Again, this table will be omitted if not useful.

5.8 Prior and Concomitant Medications

Prior and Concomitant Medications will be coded using WHO-DRL and will be assigned to the first corresponding ATC code. All medications will be listed for the safety population.
Prior medications are those medications stopped before the intake of the first dose of study Infacort® and concomitant medications are those medications taken after intake of the first dose of study Infacort®. Prior medications will only be listed.
The number and percentage of subjects with concomitant medications at baseline (i.e. medications intake started before baseline) classified by ATC levels 2 and 3 will be displayed by cohort and overall in the safety population. A similar summary will be produced for concomitant medications started after baseline (i.e., after intake of Infacort®).
However, these frequency tables (n and %) will only be provided if the number of events make such a table useful information.

5.9 Extent of Exposure

Compliance regarding the intake of Infacort® will be calculated on the basis of the number and strength of capsules dispensed, the number and strength of capsules returned, the number of days between the two visits and the daily dose of Infacort® prescribed for the time interval.
The actual daily dose of Infacort® taken will be calculated as the amount of Infacort® dispensed minus the amount of Infacort® returned divided by the number of days between the visits. The difference between planned daily dose and actually dose taken will also be calculated. Descriptive statistics for all variables will be produced by visit and overall grouped by cohort and overall for the safety population. In addition, a summary of the number and percentage of subjects who took less than 75% of the prescribed Infacort® dose and their main reasons will be presented for each cohort and overall by visit and overall. A similar summary will show the number and percentage of subjects who took more than the prescribed Infacort® dose. In addition, the number of days subjects received a correct treatment of Infacort® will be summarized by visit and overall.

5.10 Analysis of Primary Variables

All analyses will be based on the safety population. Subjects with missing information will be excluded from the analyses of the relevant variable.

Primary endpoint

The primary endpoint will be the nature and occurrence of SAEs and AEs including application of sick day rules and adrenal crises observed throughout the study. The main safety analyses are described in section 5.11 below. However, additional investigations may be performed depending on the collected information, such as time to onset of the events, relationship to another medications and/or relationship to other factors.
In any case, a summary of the number and percentage of subjects with an adrenal crises and the number and percentage of subjects with an

implementation of sick day rules and their main reasons will be presented for each cohort and overall by visit and overall.

Secondary endpoints

The secondary endpoint linear Growth Velocity (GV), in terms of cm/year, will be determined for each visit after baseline using the following equation:

$$GV = 12 * (H2 - H1) / D2$$

where H1 is the height/length (in cm) at the baseline visit (visit 1), H2 is the height/length (in cm) at the selected visit and, D2 is the time (in months) between the selected visit and baseline. The Growth Velocity-SDS (linear growth velocity standard deviation score [SDS]) or the so called z-score is then calculated by

$$Z = (GV - \mu) / SD$$

where μ is the mean value and SD the standard deviation of a age and gender matched reference population.
The growth velocity-SDS (GV-SDS) will be derived for each visit after baseline and presented by visit and overall for the safety population.

For the metabolic parameters including cortisol (all subjects) and androgens (17-OHP, A4 and testosterone) in CAH subjects only, at each scheduled time point over the course of the study (at each visit) the following will be displayed by cohort and overall: the number of subjects, mean, standard deviation, median value, and range of values (min, max). In addition, the absolute changes from baseline (last value before intake of Infacort®) will be presented, if appropriate. These summaries will be supported by a graphical presentation of values over time.
Any unscheduled laboratory evaluations will be listed only.

Additional analyses

The number and percentage of subjects for each category of the Tanner Development Stage will be displayed over time for each of the three systems [pubic hair (both sexes), breast (females), genitalia (male)] and for each cohort and overall in the safety population.
Shift tables comparing baseline (visit 1) ratings with the ratings at the interim visits will be presented for each category by cohort and overall.
Tables will be omitted, if not useful.

5.11 Analysis of Safety Variables

These analyses will be conducted for the safety population only and no formal statistical testing will be performed.
Due to the low number of subjects in this study, and depending on the reported events, several of the below mentioned tables may not provide useful information. In this case tables will be omitted.

Adverse Events

For the safety analysis only AEs with onset after the intake of Infacort® (treatment emergent AEs) will be displayed in summary tables. Events which started before intake will be listed only.
AEs will be coded using the MedDRA dictionary (version 18.1 or higher) and will be presented on the MedDRA preferred term level.

An overview summary will show both the number of events and the number of subjects for any AE, intensity (mild, moderate, severe), relationship and seriousness (yes, no).

Treatment emergent AEs will be summarized regardless of severity and relationship. Within each subject, multiple reports of events that map to a common MedDRA term (preferred term) will be condensed into a single AE.
The tables will list for each AE the number of events and the number and percentage of subjects in whom the event occurred. AEs will be grouped by system organ class (SOC).
For the summary of treatment emergent AEs by SOC, preferred term, and maximum severity, a subject who experienced more than one episode of a particular coded AE will be counted only once by the maximum severity of these episodes (preferred term). AEs with missing severity will be classified as having the highest severity.
Treatment emergent AEs classified in the CRF as related to the study medication will also be summarised by the classification, SOC and preferred term. Multiple occurrences of the same events with different relatedness will be counted once based on the highest relatedness. AEs with missing relationship will be classified as related to study drug.
All SAEs will be tabulated, if useful and listed separately. All AEs leading to withdrawal will be tabulated, if useful and all withdrawals listed including the reason for premature termination.

Clinical laboratory evaluations

For each laboratory parameter, at each scheduled time point over the course of the study (at each visit), the following will be displayed: the number of subjects, mean, standard deviation, median value, and range of values (min, max). In addition, the absolute changes from baseline (last value before intake of Infacort®) will be presented, if appropriate. For categorical parameters the number and percentage of subjects per category will be presented. Abnormal laboratory values (out of reference range) will be flagged in the listings.
Any unscheduled laboratory evaluations will be listed only.

Vital signs, Weight and Height

For each parameter (systolic blood pressure, diastolic blood pressure, pulse, temperature, weight and height/length, if available) the observed values and

changes from baseline (Visit 0) will be summarised over time by cohort and overall using descriptive statistics. In addition, z-scores based on age and gender matched reference population will be derived for the two variables height and weight and presented by visit.

5.12 Interim Analysis and Data Monitoring

An IDMC will review all safety information at regular time intervals. These formal safety reviews will be performed as specified in the IDMC SAP (see reference 4). In addition, on request of the European Medical Agency, in order to support a Marketing Authorisation Application planned for Q4/2016, a safety interim analysis will be performed 6 months after the first visit of the first subject in this study.

5.13 Revised/Additional Analysis

After the first version of this SAP, dated the 7th of March 2016 was approved a protocol amendment was issued in July 2016.
As a consequence of this amendment the following changes were made:

1) Administrative updates (the name of the Diurnal medical director was changed to [redacted] and certain references were updated)
2) The safety interim analysis requested by the European Medical Agency at 6 months was added.
3) The planned safety analyses for the IDMC will now be performed at 6 months and thereafter on a yearly basis.
4) It was felt that for the metabolic parameters a change from baseline is not always appropriate. So this was also amended.

6. REFERENCES

1)Study protocol Infacort 003: A Phase 3 open-label study of Infacort® in neonates, infants and children less than 6 years of age with adrenal insufficiency. Final version 4.0, 06.Aug.2015.

2) Study protocol Infacort 004: 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. Final version 2.0, 15.Sep.2015 and version 3.0, dated 25th of July 2016.

3) Case Record Forms. Final version 1.0, 15.Dec.2015.

4) Statistical analysis plan (SAP) with lists of tables and listings for the planned Data Safety Monitoring Reviews. Version 2.0, January 2017.

Tables and Figures

Note: Due to the low number of subjects in this study and depending on the reported events a lot of the below mentioned tables may not provide useful information. In this case tables will be omitted.

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