CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213876Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505 (b) (2)
Application Number(s)	NDA 213876
Priority or Standard	Standard
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Division/Office	DMEP/ODEII/OND
Reviewer Name(s)	William Lubas MD PhD
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Established/Proper Name	hydrocortisone oral granules
(Proposed) Trade Name	Alkindi Sprinkle
Applicant	Diurnal Limited
Dosage Form(s)	Granules in capsule for opening and oral administration
Applicant Proposed Dosing Regimen(s)	8-10 mg/m^2/day typically in three or four divided doses
Applicant Proposed Indication(s)/Population(s)	Replacement therapy of adrenal insufficiency
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Infants and children up to 18 years of age

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Glossary

AC	advisory committee
ACTH	adrenocorticotropin hormone
AE	adverse event
AI	adrenal insufficiency
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CAH	Congenital Adrenal Hyperplasia
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

The applicant is developing a formulation of hydrocortisone granules in capsules for opening and oral administration which will be referred to as Hydrocortisone granules in the rest of this review. Hydrocortisone granules are being developed as replacement therapy for use in children with adrenal insufficiency (AI) who have cortisol deficiency. The active ingredient in Hydrocortisone granules is hydrocortisone, a glucocorticoid equivalent to the human hormone cortisol. Cortisol is a stress hormone necessary to regulate blood sugar, fat and protein metabolism, which is especially important during acute illness. It has been developed as multi-particulate granules provided in hard transparent capsules which need to be opened prior to administration. It is available in doses of 0.5mg, 1 mg, 2mg and 5mg of hydrocortisone to permit more accurate dosing in children as hydrocortisone tablets currently on the US market are only available in doses of 5mg and above. The granules have been developed with a taste masking outer layer, to mask the bitter taste of hydrocortisone, to support more compliant dosing. The granules can be placed directly onto the back of the child's tongue or sprinkled onto a spoonful of food such as apple sauce or yogurt, and then washed down with water, breast milk, formula or whole milk. The capsules are transparent to allow for better visualization that all of the granules have been dispensed. The recommended replacement starting dose is 8 to 10mg/m^2/day for patients with AI alone and 10 to 15mg/m^2/day for children with congenital adrenal hyperplasia (CAH), who have AI but need higher doses to suppress adrenal androgens. The total daily dose it typically divided three times a day in growing subjects but can be adjusted to up to four or down to two times a day based on clinical response. Doses up to 25 to 30mg/m^2/day may be necessary in newborn infants with CAH to initially rapidly reduce elevated adrenal sex hormones but should be reduced as soon as possible to avoid growth suppression.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted data provide substantial evidence that Hydrocortisone granules are bioequivalent to Cortef (hydrocortisone) tablets currently indicated for the treatment of primary and secondary adrenocortical insufficiency, CAH, and other endocrine and non-endocrine conditions (not discussed in this review). In addition, the applicant submitted a single dose, open-label, PK study in children less than 6 years of age, with adrenal insufficiency, followed by a 26-month, open-label extension, to support the safety and adequacy of treatment. With chronic dosing Hydrocortisone granules were well tolerated and there were no cases of adrenal crisis, nor evidence of the need for excess sick-day rule dosing, to suggest undertreatment. In addition, the children maintained stable Standard Deviation Score (SDS) height and weight charts and stable Tanner staging suggesting no under- or over-treatment.

Therefore, the indication of "the treatment of AI" can be approved. However, as the applicant had not requested an indication "to treat excessive adrenal androgen stimulation, which is commonly seen in patients with CAH," which the Division considers as a separate and distinct indication, this second indication cannot be approved at this time.

1.3. Benefit-Risk Assessment

Appears this way on original

Benefit-Risk Integrated Assessment

Adrenal insufficiency (AI) comprises a set of conditions where the body has a deficiency in the production of the stress hormone, cortisol. AI can be primary, due to inadequate cortisol release from the adrenal cortex, or secondary, due to an inadequate stimulus from the pituitary (e.g., adrenocorticotrophic hormone (ACTH)) or hypothalamus (e.g., corticotrophin releasing hormone (CRH)) leading to an under functioning adrenal cortex. These patients are at risk especially during stressful conditions such as illnesses with fever, injury or surgery when they need elevated levels of cortisol. Under such conditions they can go into adrenal crisis with hypoglycemia, hypotension, shock and eventually death. The most common cause of primary AI in children is congenital adrenal hyperplasia (CAH) accounting for up to 70% of cases, while acquired adrenal insufficiencies such as Addison's disease make up the rest of the cases. The most common cause of CAH is 21-hydroxylase deficiency which accounts for 90% of cases with an incidence of 1 in 16,200 to 1 in 18,170 in the US. In 21-hydroxylase deficiency the accumulation of steroid precursors also results in an increase in the synthesis of adrenal androgens, which can result in virilization and ambiguous genitalia in new born females. In infants and older children excessive androgen stimulation can lead to pseudo-precocious puberty with excess growth and virilization. Patients with CAH need higher doses of glucocorticoids to feedback inhibit excess androgen production, in addition to the normal replacement doses of glucocorticoids used to treat AI. This represents a separate indication from replacement therapy for the treatment of adrenal insufficiency.

Treatment for AI involves replacement with glucocorticoids. Replacement therapy for AI was begun back in the 1950s and the glucocorticoid, hydrocortisone, under the trade name Cortef, was approved for this indication back in 1952. While there are multiple glucocorticoids that could be used for replacement, the literature shows that hydrocortisone because of its short half-life is the best choice for use in children because it limits the tendency for weight gain, dyslipidemia, diabetes and growth suppression compared to other more potent, longer acting, glucocorticoids. The problem with using Cortef tablets to treat children with AI is that the lowest available dose is 5 mg and children younger than 6 years of age typically need only a total dose of 4 to 7mg per day, which divided three times daily results in most doses needing to be between 1 and 2.5 mg. In order to get these lower doses, the tablets need to be split or crushed by a compounding pharmacy and then placed individually into capsules for sprinkling or incorporated into a liquid formulation. In general, liquid formulations are not recommended because of poor consistency with dosing, and the liquid formulation of Cortef is no longer marketed in the US. In addition, not all compounding

pharmacies are equally good at preparing accurate and uniform formulations. One reference from the literature (Neumann, U et al. 2017[1]) showed that 21% of samples from compounding pharmacies had an insufficient uniformity, and 3.6% of samples had other more potent steroids substituted for hydrocortisone. There is also a report of a 20-month-old girl with CAH who developed Cushing Syndrome from a super potent compounded formulation containing 5 to 10 times the prescribed dose on the listed label (Barillas JE et al. 2018[2]). In order to meet the need for smaller accurate doses, the applicant has developed capsules which contain 0.5, 1, 2 and 5mg of hydrocortisone manufactured to GMP standards. The capsules contain hydrocortisone formulated in small granules with a taste masking outer layer. The capsule is not meant to be swallowed but is to be opened and the contents sprinkled directly on the tongue or on apple sauce or yogurt and immediately washed down with a drink of water, milk or juice. The development of a hydrocortisone formulation which can provide smaller doses of hydrocortisone manufactured to GMP standards is a great improvement over the current practice of splitting 5mg Cortef tablets or having compounding pharmacies prepare individual capsules or liquid formulations from crushed tablets.

The clinical program demonstrated that Hydrocortisone granules are bioequivalent to Cortef in study, Infacort 007, using a cross-over study design in healthy adults. Cortef, which was originally approved in 1952, has undergone Desi Review and is currently still indicated for the treatment of both AI and CAH. The applicant did not do a similar cross over PK study in children but instead did a single dose study, Infacort 003, in 24 children less than 6 years of age with AI, 23 of which had CAH and one which had hypopituitarism. This study measured serum cortisol levels and showed adequate cortisol levels at 60 minutes post dose. Eighteen of these 24 children agreed to be followed in a long-term extension study, Infacort 004. In this study children were dosed three times daily with Hydrocortisone granules and monitored for cases of adrenal crisis and adverse events that led to sick-day rules, which required stress doses of hydrocortisone, which could represent glucocorticoid under treatment. Children were followed for more than 2 years of daily dosing. Hydrocortisone granules were well tolerated and there were no cases of adrenal crisis, nor evidence of excess sick-day rule implementation to suggest undertreatment. In addition, the children maintained stable SDS height and weight charts and stable Tanner staging suggesting no under- or over-treatment.

Drug class symptoms from over treatment with glucocorticoids include weight gain, decreased height velocity, hyperglycemia, hypertension,

[1] Neumann U, Burau D, Spielmann S, et al. **Quality of compounded hydrocortisone capsules used in the treatment of children**. Eur J Endocrinol. 2017;177(2):239-242

[2] Barillas JE, Eichner D, Van Wagoner R, Speiser PW. **Iatrogenic Cushing Syndrome in a Child with Congenital Adrenal Hyperplasia: Erroneous Compounding of Hydrocortisone.** J Clin Endocrinol Metab. 2018 Jan 1;103(1):7-11.

edema, easy bruising, muscle weakness, red round face, depression or mood swings, none of which were seen in the pediatric clinical trials. The Hydrocortisone granules seemed to be well tolerated in most children, although some younger children did seem to find the taste or texture of the granules as less palatable. Treatment related adverse events seen in the pediatric clinical trials were mostly infections (e.g. pyrexia, gastroenteritis, URI, viral infection etc.) which are common in young children over the course of a two-year study and were likely not to be drug related. However, there is a safety concern that a capsule designed for sprinkling may be inappropriately swallowed. (b) (4) there is a concern that these large capsules could represent a choking hazard in the pediatric population. In fact, the capsules were made larger partially to discourage attempts at swallowing. While there were no episodes of choking in the clinical trials or post marketing reports , the post marketing reports describe two siblings who routinely swallowed the capsules to avoid having the granules in their mouths while they were in school. So, choking from inappropriate attempts at swallowing the capsules represents a credible potential risk. While in general palatability was good for most patients, some patients like the two siblings described above did not like the taste or granule texture. There were several reports of younger children spitting up the granules, which was described as "retching" as opposed to "choking", which could result in under dosing. And five mothers withdrew their children from the open-label extension study due to the difficulty of having to give the night time dose which involved waking up the children from their sleep. The applicant believed that sleepy children might have taken longer to swallow the granules so the taste masking outer layer, which can dissolve in as little as 5 minutes, might have been removed and made them less palatable affecting compliance. Since the granules need to be washed in with a follow up drink, this also requires the child to be more conscious when woken up to avoid aspiration of the granules, which is also a potential safety concern.

In summary, this medical reviewer believes there is substantial evidence of efficacy and safety of Hydrocortisone granules for the proposed indication based on the established bioequivalence of Hydrocortisone granules with Cortef tablets, which are currently approved for the treatment of both AI and CAH . There is also supportive clinical evidence for the safe use of Hydrocortisone granules in the pediatric population, as chronic replacement therapy for adrenal insufficiency, and to support adrenal androgen suppression in children with CAH using somewhat higher doses than that would be needed to simply control adrenal insufficiency. The benefit of the current formulation to allow for more accurate dosing in younger children outweighs the theoretical risk for choking from inappropriately swallowing the capsules or under- or over-dosing from inappropriate drug administration which can be addressed with appropriate labeling and enhanced pharmacovigilance.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Primary and secondary adrenal insufficiency are due to a deficiency in the stress hormone cortisol used to regulate blood glucose, fat and protein metabolism. • Congenital adrenal hyperplasia is due to a deficiency in cortisol resulting in AI but the enzyme defect in this condition also results in excess androgen production which can result in virilization and ambiguous genitalia in new born females.	
Current Treatment Options	• While there are multiple glucocorticoids that are approved in the US for replacement therapy in adults and children with AI, hydrocortisone because of its short half-life, is the best choice for use in children because it limits the tendency for weight gain, dyslipidemia, diabetes and growth suppression compared to other more potent longer acting glucocorticoids. • Hydrocortisone tablets are currently available at doses of 5mg and above, so for children who typically need lower doses, current practice involves splitting 5mg Cortef tablets or having compounding pharmacies prepare individual capsules or liquid formulations from crushed tablets.	Hydrocortisone is the preferred glucocorticoid for the treatment of AI and CAH in children. The currently available hydrocortisone tablets are too large to provide the accurate low doses needed in younger children.
Benefit	• Hydrocortisone granules can provide 0.5, 1, 2 and 5mg doses of hydrocortisone manufactured to GMP standards which is a great improvement over splitting tablets or compounded formulations. • Hydrocortisone granules are manufactured as small granules that are easier to swallow than the currently available tablets and contain an outer layer coating to mask the bitterness of hydrocortisone. • Hydrocortisone granules were demonstrated to be bioequivalent to Cortef (hydrocortisone) tablets currently approved to treat AI and	Hydrocortisone granules provide an accurate low dose hydrocortisone formulation that can facilitate pediatric dosing. Chronic pediatric dosing for over 2 years in children with AI and CAH was not associated with evidence of substantial over- or under-treatment.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	CAH. Thus, the Applicant has established a scientific bridge allowing reliance on FDA's finding of safety and effectiveness for Cortef to support approval of Hydrocortisone granules for the treatment of pediatric AI and CAH (Study Infacort 007).	Hydrocortisone granules are bioequivalent to Cortef tablets currently approved for the treatment of AI and CAH.
Risk and Risk Management	• Hydrocortisone granules were well tolerated and there were no cases of adrenal crisis, nor evidence of excess sick-day rules to suggest undertreatment. In addition, the children maintained stable SDS height and weight charts and stable Tanner staging suggesting no under- or over-treatment during over two years of treatment. • There is a risk for choking in children who inappropriately try to swallow the large capsules. • Delay in administration beyond 5 minutes can result is loss of the taste masking outer layer affecting palatability and treatment compliance.	Product labeling needs to emphasize: • that the capsules should not be swallowed • drug administration needs to occur as soon as possible once the sprinkles are dispensed on apple sauce or yogurt and immediately washed down with water, juice or milk Enhanced pharmacovigilance should be used to monitor for adverse events resulting from drug maladministration that may need further follow up.

1.4. Patient Experience Data

The submission included responses from children and their caretakers with respect to the palatability of Hydrocortisone granules.

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1.2 Efficacy Results – Secondary and other relevant endpoints]
		X	Patient reported outcome (PRO)	
		X	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

AI refers to a condition in which there is a deficiency in the stress hormone, cortisol, which is necessary to control blood sugar levels, suppress excessive immune system response, and help regulate sugar, fat and protein metabolism. Low levels of cortisol during an acute illness can lead to an adrenal crisis, with life-threatening shock leading to death if not adequately treated. AI can be primary, due to inadequate cortisol release from the adrenal cortex, or secondary, due to an inadequate stimulus from the pituitary (e.g., adrenocorticotrophic hormone (ACTH)) or hypothalamus (e.g., corticotrophin releasing hormone (CRH)) leading to an under functioning adrenal cortex.

The most common cause of primary AI in children is congenital adrenal hyperplasia (CAH) accounting for up to 70% of cases, while acquired adrenal insufficiencies such as Addison's disease make up the rest of the cases. CAH can be due to a deficiency in one of several enzymes required for adrenal synthesis of cortisol. The most common cause is 21-hydroxylase deficiency which accounts for 90% of cases with an incidence of 1 in 16,200 to 1 in 18,170 in the US[3]. In 21-hydroxylase deficiency the accumulation of steroid precursors results in an increase in the synthesis of adrenal androgens, which can result in virilization and ambiguous genitalia in new born females. In infants and older children excessive androgen stimulation can lead to pseudo-precocious puberty with excess growth and virilization.

Secondary adrenal insufficiency can also be due congenital defects relating to the normal development of the hypothalamus and/or pituitary, or it can be acquired by injury to these vital structures due to trauma, neoplasm, surgery or cranial irradiation for example.

2.2. Analysis of Current Treatment Options

Treatment for adrenal insufficiency requires glucocorticoid replacement. Subjects with primary adrenal insufficiency and CAH also require treatment with mineralocorticoids such as fludrocortisone and sodium chloride supplements. Glucocorticoid replacement for AI started in the 1950s with cortisone and hydrocortisone tablets which have similar glucocorticoid potency (i.e. 25mg cortisone=20mg of hydrocortisone). However, cortisone requires activation in the liver by 11β-hydroxysteroid dehydrogenase which may affect its biologically activity in some subjects, so hydrocortisone has become the preferred treatment for AI in children. Also, cortisone tablets are not available at doses less than 25 mg doses, which makes them less useful in pediatric patients who require lower doses, compared to hydrocortisone tablets which

[3] Pearce M, DeMartino L, McMahon R, et al. Newborn screening for congenital adrenal hyperplasia in New York State. Mol Genet Metab Reps. 2016;7:1-7.

are currently available at doses as low as 5mg. Other more potent glucocorticoids equivalent to 20mg of hydrocortisone include prednisolone 5mg, prednisone 5mg, methylprednisolone 4mg, and dexamethasone 0.75mg which could be dosed less frequently and are used for the treatment of adults. However, these more potent glucocorticoids are more likely to cause Cushingoid symptoms. Retrospective studies in children with these more potent glucocorticoids, demonstrated a tendency for weight gain, dyslipidemia, diabetes and growth suppression so they are less frequently used in children at least as long as they are still actively growing.

The most common treatment for all causes of AI in children is hydrocortisone at doses of 8 to 10mg/m^2 administered 3 to 4 times per day. While similar doses would be adequate to treat AI in children with CAH, they need treatment with higher doses of 10 to 15mg/m^2/day to also suppress adrenal androgens. Children younger than 6 years of age typically need only 4 to 7mg total per day of hydrocortisone which divided three times daily results in most doses needing to be between 1 and 2.5 mg. A hydrocortisone liquid suspension of Cortef was once available in the US but is no longer marketed. Therefore, hydrocortisone is only currently available in tablet formulation for oral administration, with the lowest available dose of 5mg. That means that parents need to split or crush the 5mg tablets to supply the required doses. This can result in under- or over-dosing during the day. In addition, these crushed tablets have a bitter taste which makes compliant dosing difficult. Compounding pharmacies can make individual capsule or liquid formulations but there are reports of variable dose accuracy in compounded preparations[1,2]. Symptoms of undertreatment for AI could include nausea, decreased appetite, weight loss, fatigue, abdominal pain, vomiting, hypoglycemia, hyperpigmentation, difficulty concentrating. Children with CAH may also show signs of androgen excess such as pubic hair, underarm hair, body odor, acne, clitoromegaly, growth of the phallus, bone age acceleration due to undertreatment. Symptoms of over treatment include weight gain, decreased height velocity, hyperglycemia, hypertension, edema, easy bruising, muscle weakness, red round face, depression or mood swings. Children with CAH are more susceptible to diabetes, obesity and hypertension from overtreatment due to use of glucocorticoids in supraphysiologic doses to suppress androgen excess.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cortef (hydrocortisone) tablets were approved in the US in 1952 and are currently available at doses of 5, 10 and 20mg for the treatment of primary and secondary adrenocortical insufficiency in addition to a variety of indications related to its potent anti-inflammatory activity. The applicant is only seeking the indication for replacement therapy of adrenal

insufficiency in infants, children and adolescents (from birth to < 17 years of age) and not the separate indication "to treat excessive adrenal androgen stimulation, which is commonly seen in patients with CAH," which the Division considers as a separate and distinct indication. Hydrocortisone granules is not approved in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

The sponsor submitted a PreIND meeting (PIND 123322) request on 25 March 2015 to discuss their developmental program for the treatment of pediatric AI and CAH. The Agency responded with written responses on 22 May 2015 stating that the sponsor's proposal to seek approval via the 505(b)(2) pathway was reasonable. The sponsor was informed that they would need to identify the listed drug(s) to be used to support previous findings of safety and effectiveness and to establish a "bridge" between their product and the listed drug(s) that was scientifically justified. The Agency did not agree with "maximum levels of serum cortisol concentration after intake of study drug…" as the primary endpoint for their proposed pivotal study, Infacort 003, and recommended instead that the study include PK endpoints of AUC, C_{max}, and C_{trough} for cortisol and any other clinically relevant parameters the sponsor may choose to use. In addition, since the Agency was concerned that infants and younger children might have the sprinkle formulation mixed into water, breast milk, baby formula or pureed foods the sponsor was asked to include a food effect study in healthy adults to address representative vehicles such as pureed food, water and baby formula. The Agency also requested the sponsor to provide in-use stability data if the sprinkled formulation was to be stored in the various food vehicles prior to administration.

The sponsor did not follow all of the Agency's advice, dealing with changes to the design of Infacort 003, and instead completed their clinical program in the European Union (EU) where they first sought and later received marketing approval in 2018.

On 6 Feb. 2019 the sponsor met with the Agency in a "Type C" meeting to discuss plans for a 505(b)(2) literature-based NDA for the treatment of pediatric adrenal insufficiency. At the time of the meeting all of the clinical studies (Infacort 001, 002, 003, 004, 006 and 007) had already been completed in the EU.

- The Agency reviewed the completed clinical program and agreed that the data might be sufficient to support the proposed indication but that the final decision would be a review issue.
- The sponsor stated that they planned to use their bioequivalence study to bridge safety and efficacy information to the reference listed drug Cortef (NDA 008697).
- The hydrocortisone product used in the original Infacort studies 001 and 002 was a UK product, but a US product was used in the later studies. The Agency stated this should be acceptable, but the final decision would be a review issue.

- The sponsor confirmed that, while hydrocortisone is approved for a number of different indications, they were only seeking an indication for replacement therapy in pediatric adrenal insufficiency.
- The Agency agreed to the small sample size of the study population if additional efficacy and safety information could be submitted from publications to support the clinical efficacy and safety for this indication.
- The sponsor proposed to use the Endocrine Society guidelines of dosing 3 to 4 times daily for the treatment of AI in children, with the exact dosing regimen to be determined by the prescribing endocrinologist.
- The Agency expressed their concerns that the capsule may be swallowed inadvertently even though it is not meant for consumption. They asked the sponsor to provide their rationale for the proposed presentation and any information on any efficacy or safety concerns which were identified with users swallowing the product (b) (4) . The sponsor stated that the capsules had been used in the EU for two years in clinical trials and had been marketed since May 2018 with no reports of choking. The sponsor agreed to submit updated postmarketing data concerning the choking risk at the time of the NDA submission.
- The sponsor proposed to submit in-vitro dissolution information to support that the capsules behave as an immediate-release formulation in the case they are swallowed inadvertently.
- The Agency asked the sponsor to provide mitigation strategies to ensure users understand how to select the appropriate dose strength if the small number of dosage strengths (0.5-, 1-, 2- and 5-mg) were not adequate to administer the recommended dose. The sponsor proposed when calculating the dose that prescribers should round up or down to the nearest 0.5 or 1mg dose.
- The sponsor said they did not intend the product to be administered via a feeding tube (b) (4)

The sponsor requested a PreNDA meeting with the Agency on 17 April 2019 to discuss summary tabulations to be included in the clinical safety and efficacy sections of their NDA. The Agency responded with a Written Responses Only letter dated 15 May 2019 addressing the sponsor's concerns:

- The Agency agreed with the sponsor's proposed format for supplying information in the integrated summary of clinical efficacy (ISE) and integrated summary of clinical safety (ISS).
- The Agency asked the sponsor to summarize clinical data in the NDA submission by age subgroup 0-28 days, > 28days to ≤ 2years, >2 to ≤ 6 years and > 6 years to ≤ 18 years.

Orphan drug designation for this product for the treatment of pediatric adrenal insufficiency (0 through 16 years of age) # 14-4416 was granted by the FDA on 13 May 2015.

3.3. Foreign Regulatory Actions and Marketing History

Infacort was granted a marketing authorization by the European Commission in February 2018 under the name Alkindi at doses of 0.5, 1, 2 and 5mg for a similar indication "replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to < 18 years of age). But under Posology: "*Replacement therapy in primary and secondary adrenal insufficiency*", they recommend higher CAH specific dosing without mentioning that the need for the higher doses is to treat excess androgen production and not just to control adrenal insufficiency.

Medical officer's comments-In contrast to the EU, the Division of General Endocrinology (DGE) sees the need to treat with higher doses to address virilization associated with excess androgen production as a separate indication from the indication to treat primary and secondary AI.

Total worldwide volume of sales for Alkindi, estimated in terms of the maximum number of patients treated, is (b) (4) since launch in Germany, UK, Austria, Denmark, Iceland, Norway and Sweden.

Table 1. Worldwide Market Authorization Status for Alkindi

Country	Action	Date of Action	Date of Commercialisation	Invented Name	Indication
Germany	A	09FEB2018	(b) (4)	Alkindi	Replacement therapy of AI in infants, children and adolescents (from birth to < 18 years old)
UK					
Austria					
Denmark					
Sweden					
Iceland					
Norway					

Key: Action- A (Approval), Q (Approval with Qualification), R (Rejection), V (Voluntary withdrawal by Diurnal Europe B.V.) S (Suspension by Regulatory Authority), R (Renewal)

Source NDA 213876 SDN 001 Section 5.3.6 EU PBRER #3 Table 1, pg 7

Three European PBRERs were provided with the current submission (See SDN001, Section 5.3.6) covering the marketing period from February 2018 through August 2019.

Table 2. Alkindi Worldwide Sales Data

	Alkindi 0.5 mg (hydrocortisone) 50 count single bottle	Alkindi 1 mg (hydrocortisone) 50 count single bottle	Alkindi 2 mg (hydrocortisone) 50 count single bottle	Alkindi 5 mg (hydrocortisone) 50 count single bottle	**Estimated patient exposure**
PBRER #1 Units shipped	(b) (4)				
PBRER #2 Units shipped					
PBRER #3 Units shipped					
Cumulative Units shipped					

Source NDA 213876 SDN 001 Section 5.3.6 EU PBRER #3 Table 4, pg 10

The updated summary of safety concerns from the latest PBRER #3 is listed below in Table 3. There have been no changes to the benefit profile and no new identified or potential risks raised since initial marketing according to the applicant. The important identified risks deal with well recognized conditions seen in children treated with steroids chronically and are not specific to the Alkindi capsule/sprinkle formulation. The potential risks of choking on the capsule, and aspiration of granules are specific to the Alkindi formulation (see highlights below).

Table 3. Summary of Safety Concerns from PBRER #3

Summary of safety concerns	
Important identified risks	Growth Retardation Acute Psychiatric Effects Reduced Bone Mineral Density and Risk of Bone Fractures Drug-drug interactions (with CYP3A4 enzyme inducers and CYP3A4 inhibitors)
Important potential risks	Choking on the capsule Accidental Underdose Aspiration of Granules Drug-drug interactions seen only at high doses of Hydrocortisone (with aspirin, coumarins, diuretics, anti-hypertensives, drugs or substances causing hypokalaemia, hypoglycaemic agents) Risk of Central Serous Chorioretinopathy
Missing information	Long Term Use in Paediatric Patients Use in Hepatic Impairment Use in Renal Impairment

Source NDA 213876 SDN 001 Section 5.3.6 EU PBRER #3 Table 5, pg 37

PBRER #1 Feb. 2018 to Aug. 2018
There was one non-serious post-marketing report in a female infant with Adrenogenital syndrome who reported anxiety, diarrhea and fatigue. Alkindi was withdrawn after three days of treatment and the event of anxiety recovered after four days.

PBRER #2 Aug. 2018 to Feb. 2019
There was one serious report of bloody diarrhea which included nonserious reports of "choking and coughing post-dosing in a 3-week old infant", "difficult to swallow", "gagging on medication" and "underdose". The applicant felt there was some confusion about the terminology used to describe the case due to the need for a German translation and believed that the episode did not indicate "choking and coughing" but rather "difficulty in dosing a child". A similar report had been received during clinical study Infacort 004 (Subject (b) (6) according to the applicant, and follow up of that case provided the following explanation:

> *"If we say choking we mean to gag or retch. There was no child where we had the suspicion of choking in the sense of that the child got granules into the lung and could not breathe"*. It was confirmed that "verschlucken" is often used colloquially to refer to either choking, aspiration or gagging. Paediatricians are very familiar with children refusing medication even as infants by protruding their tongue to expel the medicine or gagging or retching on the medicine, or even sometimes before the medicine is even administered. These reactions are not the same as choking and though they may raise a concern about under dosing or failure to administer a dose, they do not raise the risk of aspiration.

Therefore, this case was reclassified as "retching" under post-marketing data sources.

There was also one nonserious report of "medication error" reported in a 2-week-old neonate who had Alkindi granules spread onto their lips rather than administered into the mouth on the tongue. No adverse events were associated with this case.

PBRER #3 Feb. 2019 to Aug. 2019
There were three reports containing one non-serious event each of hypersensitivity (Case ID: DE-DIURNAL2-(b) (6)), malaise (Case ID: GB-DIURNAL2-(b) (6)), and abnormal feces (Case ID: DE-DIURNAL2-(b) (6)). Alkindi was withdrawn in the patient who experienced hypersensitivity after an unknown duration of treatment. Information was not included about the other cases.

There was also one case of "medication error" (Case ID: GB-DIURNAL2-(b) (6) in an 8-year-old female patient who experienced difficulty administering Alkindi. The patient ended up spilling the contents of the Alkindi capsule as it was so full. When the patient tipped the granules into her mouth it got stuck around the rim of the capsule. No adverse events were associated with this "medication error".

There was one report of "intentional product misuse" (Case ID: DE-DIURNAL2-(b) (6)) in a case regarding a 12-year old male patient whose mother combined the patient's midday dose into a single capsule, so the patient only needed to take one capsule to school. This was an intentional product misuse and no adverse events were associated with this report.

There was also one report of "product dispensing error" (Case ID: GB-DIURNAL2-(b) (6) reported by a healthcare professional regarding a pharmacist who transferred Alkindi into a new bottle. It was not clear whether a package insert was provided. The patient (age unknown) took the product and did not experience any adverse events.

PBRER #4 Aug. 2019 to Feb. 2020 (120-day 3.0 SDN 6)
There was one non-serious report of nausea (Case ID: SE-DIURNAL2-(b) (6)) in a female of unknown age. Alkindi was withdrawn and the event was reported as resolved.

There was one report of retching (Case ID: DE-DIURNAL2-(b) (6) in a 6-month old baby who experienced gagging following the administration of Alkindi. The baby was switched back to compounded hydrocortisone dissolved in liquid which was administered with a syringe. As this report was identified on a patient group internet forum no follow up was possible and thus additional information is not expected.

There was one report of underdose (Case ID: DE-DIURNAL2-(b) (6)) in a new-born female patient whose medication was switched from intravenous hydrocortisone to oral Alkindi granules in capsules for oral administration. It was reported that half an hour after administration, the patient spat "something" out. The patient's cortisone level at check-up was reported as too low (under 15 mg per m^2); therefore: intravenous hydrocortisone was restarted and upon check-up, the cortisone level was found to be okay. Alkindi was withdrawn.

There were two reports of "medication errors" (Case IDs: DE-DIURNAL2-(b) (6) and DE-DIURNAL2-(b) (6)) in two siblings of unknown age and gender who routinely swallow the whole Alkindi capsule rather than opening them and administering the granules, as both siblings do not like that the granules get stuck in their mouths when taking Alkindi at school. There were no adverse events associated with these reports. According to the report this was unsurprising as the Alkindi capsule (b) (4) although not recommended by Diurnal, due to the size of the capsule being difficult to swallow, dosing in this manner would not alter the dose received by the patient.

> *Medical officer's comments- There are clear examples of medication errors with the administration of this product. None of which were considered serious.*
>
> *Most concerning were the cases of children swallowing the capsules instead of opening them because they did not like the granules getting stuck in their mouths and the*

episodes of "retching", which in one case was initially described as "choking", and probably represented difficulty with swallowing the granules and was not due to aspiration of the capsule contents.

Given that this medication is to be given to neonates, many with poor suck reflexes at birth, spitting up may also be a relevant issue, although a crushed hydrocortisone tablet is likely to present similar problems during oral administration.

The inability to get all of the granules out of the capsule after wetting the rim with saliva is more likely to occur if the capsule is used to pour the granules on the tongue instead of first being opened onto a spoon. This issue can adequately be addressed with labeling.

Capsules should not be used to pool doses. This could result in loss of drug product due to spillage or inappropriate dosing if the capsule's actual contents are not clearly marked and mixed up with standard capsules. This issue can adequately be addressed with labeling.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Infacort 007, the bioequivalence study comparing Hydrocortisone granules to Cortef tablets was the only study for which an OSI edit was requested as studies Infacort 003 and 004 were not considered pivotal studies. An onsite inspection was not possible for the clinical portion of study Infacort 007 due to the disruption of inspectional activities by the COVID-19 global pandemic. OSI instead conducted a remote record review. Based on the findings of the remote record review dated 27 August 2020, OSI concluded the data from the audited studies are reliable.

4.2. Product Quality

Hydrocortisone granules are an immediate release formulation of hydrocortisone for use in the pediatric population. It is formulated with a hard capsule container containing immediate release multiparticulate granules that is to be opened to permit release of the granules directly onto the top, and towards the back, of the child's tongue. The hard capsule is not intended for consumption. Alkinidi is available in dose strengths of 0.5 mg, 1 mg, 2 mg and 5 mg hydrocortisone. All excipients used in Hydrocortisone granules have Generally Recognized As

Safe (GRAS) approval status. (b) (4)

All Office of Pharmaceutical Quality (OPQ) disciplines have completed their assessments and recommend approval.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical studies submitted in the submission. Reference is made to published literature for hydrocortisone. All excipients are GRAS and impurities were consistent with the referenced product. Hydrocortisone granules are intended as replacement therapy in AI and with slightly higher levels to control androgen hormone secretion in CAH, but serum levels are expected to be well below the pharmacological levels that are likely needed for anti-inflammatory and immunosuppressive effects.

4.5. Clinical Pharmacology

The Hydrocortisone granule development program included:

- several Phase 1 studies, Infacort 001 and Infacort 002 in normal, healthy adult volunteers evaluating bioequivalence to hydrocortisone 10 mg and 20 mg tablets and dose linearity from 0.5 mg to 10 mg.
- study Infacort 007, which was designed to evaluate bioequivalence of Hydrocortisone granules to the US approved product Cortef, and
- PBPK modeling, comparing pediatric and adult pharmacokinetics

Infacort 007- A two-part, single centre, open-label, randomised, single-dose, two period, crossover relative bioavailability study of Infacort versus Cortef in dexamethasone-suppressed healthy adult male and female subjects in the fasted and fed states.

Study Infacort 007 was performed to bridge Hydrocortisone granules to the US reference immediate release hydrocortisone product, Cortef. It consisted of a two-part, single center, open-label, randomized, two-period, crossover, bioavailability study of Hydrocortisone granules versus Cortef in dexamethasone suppressed healthy adults in fed and fasted states. C_{max} was

decreased for both drugs in the fed state but AUC was relatively unaffected. T_{max} was slightly sooner with the Hydrocortisone granules compared to the Cortef tablets (mean 45 min vs. 60 min fasted and mean 75 min vs. 90 min fed) but the difference is unlikely to be clinically relevant.

Table 4. Baseline-Adjusted Cortisol PK Parameters in Study Infacort 007 (PK Dataset)

	C_{max} (nmol/L)	T_{max} (hours)	AUC_{0-t} (h*nmol/L)	AUC_{0-inf} (h*nmol/L)
Infacort fasted (N=24)				
Median (range)	1200 (705, 2480)	0.750 (0.500, 1.50)	3300 (1700, 12900)	3330 (1780, 14500)
Geometric mean	1310	NA	3970	4090
Cortef fasted (N=24)				
Median (range)	1080 (686, 2290)	1.00 (0.500, 2.50)	3720 (2210, 11600)	3770 (2250, 13100)
Geometric mean	1190	NA	4200	4340
Infacort fed (N=24)				
Median (range)	725 (505, 1370)	1.25 (0.500, 3.00)	3360 (2240, 8970)	3380 (2240, 9560)
Geometric mean	727	NA	3560	3620
Cortef fed (N=24)				
Median (range)	785 (482, 1710)	1.50 (0.250, 5.00)	3220 (1850, 7600)	3290 (2480, 7830)[1]
Geometric mean	803	NA	3370	3490

AUC_{0-inf} = area under the serum concentration-time curve from time 0 to infinity, AUC_{0-t} = area under the serum concentration-time curve from time 0 to time t, C_{max} = maximum serum concentration, NA = not applicable, PK = pharmacokinetic, T_{max} = time to maximum serum concentration

[1] n=23

Source Table S1 Synopsis Study Infacort 007

Overall exposure data (AUC_{0-t}, AUC_{0-inf} and C_{max} values) showed that Hydrocortisone granules were bioequivalent to Cortef, as evidenced by the 90% CIs that were within the 80% to 125% limits in both the fasted and fed states.

Table 5. Summary Statistical Analysis of Baseline-Adjusted Relative Cortisol Bioavailability in Study Infacort 007 (PK Dataset)

	Infacort/Cortef Ratio and 90% CI	
Parameter	Part 1: fasted (N=24)	Part 2: fed (N=24)
C_{max} (nmol/L)	109.54 (102.07, 117.55)	90.53 (83.14, 98.59)
AUC_{0-t} (h*nmol/L)	94.68 (88.12, 101.72)	105.83 (100.34, 111.61)
AUC_{0-inf} (h*nmol/L)	94.26 (87.56, 101.46)	104.50 (99.50, 109.75)[1]
	Median Difference and 95% CI	
T_{max} (hours)	-0.38 (-0.50, -0.25)	-0.25 (-0.75, 0.25)

AUC_{0-inf} = area under the serum concentration-time curve from time 0 to infinity, AUC_{0-t} = area under the serum concentration-time curve from time 0 to time t, CI = confidence interval; C_{max} = maximum serum concentration; PK = pharmacokinetic; T_{max} = time to maximum serum concentration

[1] n=23

Source Table S2 Synopsis Study Infacort 007

Infacort 003 (single dose) and Infacort 004 (open-label extension) were Phase 3 studies designed to confirm that administration of Hydrocortisone granules to neonates, infants and children less than 6 years of age will provide adequate absorption of hydrocortisone. They were supposed to gather pediatric population PK data. Of these only study Infacort 003 gathered limited PK data.

Medical officer's comment- Adult PK data suggest Hydrocortisone granules are bioequivalent to Cortef. However, there is limited PK data in the pediatric population, and PK/PD modeling discussed below suggest faster drug elimination in neonates and children < 2 years of age. Clinically this suggests younger children may need more frequent dosing to maintain effective drug levels.

DEVELOPMENT OF A PHYSIOLOGICALLY BASED PHARMCOKINETICS (PBPK) MODEL FOR INFACORT WITHIN THE SIMCYP POPULATION-BASED SIMULATOR AND SUBSEQUENT PREDICTION OF PHARMACOKINETIC PARAMETERS AND DOSES IN PAEDIATRIC POPULATIONS

A PBPK model was developed for hydrocortisone incorporating both non-linear blood to plasma ratio and protein binding using the Advanced Dissolution, Absorption and Metabolism (ADAM) model already built within Simcyp. The model was verified in the adult population based on published clinical studies and the Infacort-001, -002 and -006 clinical trial data and then tested in pediatric age ranges. In the pediatric model, the ontogeny data for 11β-HSD2 and 5α-reductase was entered into the model and the PK profiles predicted in the pediatric population.

In the adult population the predicted/observed $AUC_{0\text{-}inf}$ ratio was within 0.8 to 1.25-fold in all cases and predicted values were within the 99.998% confidence interval (CI) around the observed geometric mean. The predicted/observed C_{max} was always within 2-fold of the predicted value and in 71% of cases was within 0.8 to 1.25-fold, with predicted values within the 99.998% confidence interval (CI) around the observed geometric mean. There is some under-prediction of Cmax particularly in the 0.5mg and 2mg single doses. The previously reported non-linearity in PK parameters across the 0.5 to 20mg dose was predicted well by the model according to the applicant.

In the pediatric model over 90% of the observed concentration-time Infacort 003 data was within the 5th and 95th percentiles for the predicted data in the <1-month, 1-month to 2 years and 2 to 6 years age bands. Allometric corrections appeared to adequately account for doses equivalents in children 6 years of age and older, although there was no clinical data in this age group. So, an adult (i.e. > 18 years of age) dose of 20mg was equivalent to 20mg in children 16 to < 18 years of age, 15mg for children 12 to < 16 years of age, and 10mg for children 6 to <12years of age at approximately 0.3mg/kg or 10mg/m^2 (see Table 6). However younger age groups appear to have faster elimination of hydrocortisone and so require higher mg/kg doses to be equivalent to 20mg in adults. Equivalent dosage in children 0 to <1month would be 1mg/kg (2.3-fold higher), in children 1m to <2years of age would be 0.69mg/kg (1.3-fold higher), and in children 2 to <6years of age would be 0.36mg/kg (0.2-fold higher).

Table 6 Summary of PBPK and Allometric Scaling of Hydrocortisone Granules Doses in Pediatric Age Groups Equivalent to 20mg in Adults

Age range (years)	Body weight (kg)	BSA (m^2)	PBPK model dose			Allometric scaled dose (nearest mg)		
			mg	mg/kg	mg/m^2	mg	mg/kg	mg/m^2
0.044 to 0.071*	3.8	0.24	3.9	1.04	16.2	2.2	0.58	9.1
0.3 to 1.8*	10.3	0.48	7.2	0.69	14.9	4.7	0.45	9.8
2 to 4.7*	15.6	0.66	5.7	0.36	8.6	6.4	0.41	9.7
6 to <12	28.4	1.0	10	0.35	9.6	10	0.35	9.6
12 to <16	49.3	1.5	15	0.30	10.0	15	0.31	10.1
16 to <18	61.2	1.7	20	0.33	11.7	18	0.29	10.4
20 to <25	71.5	1.8	20	0.28	10.9	20	0.28	10.9

Medical officer's comments- Children under 2 years of age appear to have a much higher clearance for hydrocortisone. Treatment guidelines do recommend higher doses for children under 1 month of age to prevent hypoglycemia and to "reduce markedly elevated adrenal hormone levels, but it is important to rapidly reduce the dose when target levels are achieved[4]". It maybe that this recommendation for higher dosing in neonates is also taking into account the 2.3-fold higher clearance. Children 1 month to 2 years of age also have a higher clearance of 1.3-fold relative to older children and adults. While higher starting dosages are not recommended in this age group it seems reasonable that they could require more frequent dosing to compensate for the more rapid drug elimination. Guidelines currently recommend dosing three to four times a day in growing children while dosing two or three times a day appears to be adequate in fully grown children[4]. Also, while treatment guidelines recommend a range of 10 to 15mg/m^2/day for starting doses for the treatment of children with CAH, dose adjustment depends on clinical response looking at linear growth, weight gain and laboratory values when appropriate. So, it is possible that children under 24 months of age may end up being treated with relatively higher doses in the recommended dose range in order to maintain an adequate clinical response. Note in Figure 3 below, which plotted dose by Body Surface Area (mg/m^2) versus age in months, children 1 to 24 months were all dosed at ≥10mg/m^2/day while some of the older children over 24 months of age were adequately treated with lower doses < 10mg/m^2/day.

[4] Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, White PC **Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline** J Clin Endocrinol Metab 2018 Nov 1;103(11):4043-4088

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Given the concern over a possible choking hazard if the capsules were swallowed inappropriately, the review team with consultation with DMEPA and OSE initially asked the sponsor to consider a Human Factors Study to address the potential risk. However, after further review it was decided that the risk did not represent a new or unique risk as compared to other similar products and based on our postmarket experience with similar products it was determined that a Human Factors Study was not required to support the marketing application (see T-con meeting minutes 22 August 2019).

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product; Dosage; Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA/BE, PK	Infacort 001	Module 5.3.1.2	Primary: To compare the PK of Infacort® vs. IRHC at a single dose of 10 mg and to determine the dose proportionality for Infacort at doses of 0.5 mg, 2 mg, 5 mg and 10 mg	Single center, open-label, randomized, 5-way crossover study IRHC tablet (EU sourced)	Infacort granules at doses of 0.5 mg, 2 mg, 5 mg and 10 mg given orally as a single dose IRHC 10 mg tablet given orally as a single dose	16	Healthy subjects	Single dose	Complete; Full
BA/BE, PK	Infacort 002	Module 5.3.1.2	Primary: To determine the absolute bioavailability of cortisol from Infacort granules and hydrocortisone tablets using i.v. hydrocortisone as the reference injection. To determine the comparative bioavailability of cortisol from Infacort granules with the reference hydrocortisone tablets.	Single center, open-label, partially randomized, 5-way crossover study IRHC tablet (EU sourced) and i.v. hydrocortisone No IMP and dexamethasone also evaluated	Infacort 20 mg granules given orally as a single dose IRHC 20 mg tablet given orally as a single dose or hydrocortisone 100 mg/mL solution for i.v. injection given as a single dose	14	Healthy subjects	Single dose	Complete; Full
Safety and efficacy	Infacort 003	Module 5.3.5.2	Primary: To demonstrate significant absorption of hydrocortisone from the Infacort preparation	Single center, open-label, single dose study No control	Infacort granules given orally as a single dose, with the dose being equivalent to the previous day's morning dose	24	Subjects <6 years old with a diagnosis of AI and a clinical need for cortisol replacement therapy	Single dose	Complete; Full
Safety and efficacy	Infacort 004	Module 5.3.5.2	Primary: To gather data on the long-term safety and efficacy of Infacort in subjects completing study Infacort 003	Open-label, non-randomized, observational study No control	Infacort granules given orally at the clinically appropriate dose (usually 3 or 4 times a day)	18	Subjects previously enrolled in study Infacort 003	Until subject withdrawal or Infacort commercially available locally (which has now been achieved)	Complete; Full
BA/BE, PK	Infacort 006	Module 5.3.1.1	Primary: To evaluate bioavailability of Infacort administered as sprinkles (multiparticulate granules) with soft food and yogurt compared with direct administration to the back of the tongue	Single center, open-label, randomized, 3-period crossover study No control	Infacort 5 mg granules given orally as a single dose either dry, sprinkled onto soft food, or sprinkled onto yogurt	19	Healthy subjects	Single dose	Complete; Full
BA/BE, PK	Infacort 007	Module 5.3.1.2	Primary: To determine the relative bioavailability of Infacort compared with Cortef® based on serum cortisol in both fasted and fed states	Single center, open-label, randomized, 2-part, 2-period crossover study Cortef	Infacort 20 mg granules given orally as a single dose in either a fasted or fed state Cortef 20 mg tablet given orally as a single dose in either a fasted or fed state	51	Healthy subjects	Single dose	Complete; Full

AI=adrenal insufficiency; BA=bioavailability; BE=bioequivalence; EU=European Union; IMP=investigational medicinal product; IRHC=immediate-release hydrocortisone; i.v.=intravenous; PK=pharmacokinetic(s)

Source: Table 5.2-1 Tabular Listing of all Clinical Studies

5.2. Review Strategy

Literature is used to support the use of Cortef (hydrocortisone) for the treatment of AI in children and as the primary source for dosing information for this indication. The Phase 1 study, Infacort 007, in healthy adult volunteers, is the pivotal study used in the Hydrocortisone granules development program to demonstrate bioequivalence to Cortef and thereby to support the indication for replacement therapy in AI. In addition, the clinical program included two supportive clinical studies in children with AI:

- Infacort 003, which was a single dose study and demonstrated adequate serum cortisol levels in neonates, infants and children less than 6 years of age with AI at 60 minutes post dosing and
- Infacort 004, which demonstrated no episodes of adrenal crisis, and stable growth and development in children with AI, during a period of over 2 years of chronic treatment with Hydrocortisone granules.

Data is presented using the applicant's tables and figures when appropriate, as well as this medical reviewer's analysis of the applicant's data set using JMP software. In all cases the source of the data is listed at the bottom of each table or figure.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Literature to support the efficacy of hydrocortisone for the treatment of AI and CAH

Treatment of CAH due to 21-hydroxylase deficiency with glucocorticoid replacement therapy began in the 1950s (New 1998[5]). Replacing the deficient hormone, cortisol, with an effective glucocorticoid, addresses both AI symptoms and results in feedback inhibition of the release of ACTH from the pituitary, suppressing overproduction of adrenal androgens preventing further virilization, slowing accelerated growth and bone-age advancement to a more normal rate, and allowing a normal onset of puberty. Hydrocortisone (cortisol) is the preferred glucocorticoid during childhood because of its short half-life which minimizes the adverse effects typically seen with longer acting and more potent agents such as prednisolone or dexamethasone, which can lead to growth suppression (Speiser et al. 2018[4]). In randomized trials Silva et al. 1997[6] demonstrated that while doses of hydrocortisone as high as 25mg/m^2/day did not fully suppress or normalize production of 17-hydroxyprogesterone (17-OHP) and adrenal androgens,

[5] New, MI, **Diagnosis and Management of Congenital Adrenal Hyperplasia** Annu. Rev. Med. 1998, 49:11-28
[6] Silva IN, Kater CE, Cunha CF, Viana MB. **Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia.** Arch Dis Child. 1997 Sep;77(3):214-8.

such high doses had a harmful effect on growth velocity. They therefore recommended doses less than 15mg/m^2/day to minimize the effect on growth suppression and recommended against attempting to normalize plasma 17-OHP concentrations. Dosing three to four times a day better mimics the circadian rhythm and may be beneficial to counter long term complications of glucocorticoid replacement (Bornstein et al. 2016[7]). Taking this information into account the Endocrine Society currently recommends dosing hydrocortisone at 10 to 15mg/m^2/day three times a day in growing children with CAH but allows for less frequent, twice daily dosing, in subjects who are fully grown (Speiser et al. 2018[4]). Glucocorticoid replacement therapy is also effective for the treatment of other causes of both primary and secondary adrenal insufficiency. The daily basal cortisol production rate in children has been shown to range between 6.1 ± 1.8 mg/m^2/day in boys to 7.3 ± 1.8 mg/m^2/day in girls (Linder et al. 1990[8]). So, children with primary AI not due to CAH, who do not need to address elevated adrenal hormone levels, can be treated with lower doses of hydrocortisone. Taking into account the variable bioavailability of oral hydrocortisone formulations due to incomplete intestinal absorption and hepatic metabolism, children with AI alone can be adequately treated with doses 8 to 10mg/m^2/day or less depending on their level of endogenous cortisol secretion (Bornstein et al. 2016[7]). In general, the goal of therapy is to control symptoms of AI with the lowest possible hydrocortisone dose, without compromising growth as is seen with overtreatment.

6.2. **Study Infacort 003**-A PHASE 3 OPEN-LABEL STUDY OF INFACORT IN NEONATES, INFANTS AND CHILDREN LESS THAN 6 YEARS OF AGE WITH ADRENAL INSUFFICIENCY

6.2.1. Study Design

Overview and Objective

Study Infacort 003 was designed as a single dose study to assess PK, safety, effectiveness and tolerability of Hydrocortisone granules in the target pediatric population. Patients who completed this single dose study were encouraged to enroll into an open-label long term extension study Infacort 004 to assess safety and effectiveness with chronic dosing.

Trial Design Infacort 003

Infacort 003 was a single center, open-label, single dose study of Hydrocortisone granules in children less than 6 years of age that required corticosteroid replacement therapy for adrenal

[7] Bornstein AR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ **Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline** J Clin Endocrinol Metab Feb 2016, 101(2):364-389

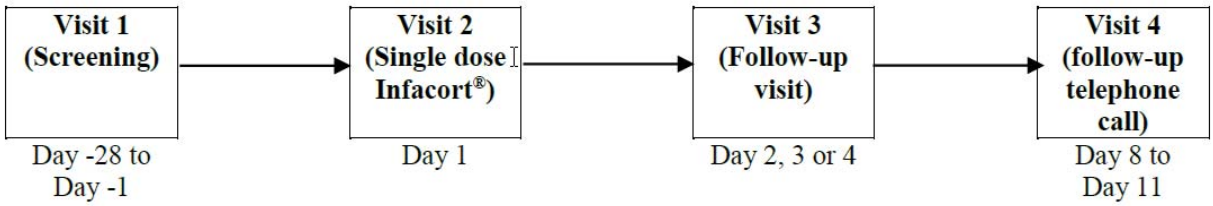
[8] Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F **Cortisol production rate in childhood and adolescence** J Pediatr 1990 Dec;117(6):892-6.

insufficiency due to either CAH, primary adrenal failure or hypopituitarism. The study consisted of three consecutive cohorts, distinguished by age at time of treatment:

- Cohort 1- ages 2 to < 6 years (n=12)
- Cohort 2- ages 28 days to < 2 years (n=6)
- Cohort 3- neonates to < 28 days (n=6)

Enrollment in each subsequent cohort was to occur if no safety concerns were observed in the first 6 patients treated in the previous cohort.

Figure 1. Study Design for Infacort 003



Source Figure 1. Infacort 003 Clinical Study Report

> *Medical officer's comment- The open-label nature of the study should not significantly impact on the study results. Assuming there is no difference in bioavailability between the adult and pediatric population, a single-dose PK study with population PK in the pediatric population should be adequate to assess drug levels, as hydrocortisone does not accumulate with repeat dosing. However, a single dose study is limited with respect to safety data, therefore the applicant encouraged children in this study to also enroll in the open-label extension study Infacort 004 to assess safety with chronic dosing.*

Inclusion Criteria-including but not limited to:

1. Male and female children less than 6 years of age.
2. Diagnosis of AI confirmed by an inappropriately low cortisol level and other supporting tests.
3. Currently receiving adrenocortical replacement therapy (hydrocortisone with/without fludrocortisone).

Exclusion Criteria-including but not limited to:

1. Ongoing active adrenal crisis
2. Inability to take oral therapy
3. Concomitant therapy other than that required to treat AI. Treatment with vitamin D, fluoride, thyroxine and growth hormone were acceptable.
4. Clinical signs of acute infection or fever on Day 1.
5. Any surgical or medical condition which in the opinion of the Investigator may have placed

the subject at higher risk from their participation in the study.

Medical officer's comment-The inclusion/exclusion criteria were appropriate.

On study day 1 subjects had to fast for at least 2 hours (45 minutes for children age <1 year) before dosing and were asked not to eat until after the sampling at 60 minutes (30 minutes for children age <1 year). Subjects received the equivalent dose of Hydrocortisone granules as their usual dose of hydrocortisone tablets and at the same time of day. Hydrocortisone granules capsules as needed were opened and the entire contents sprinkled on the back of the child's tongue and then washed down with water, breast milk, formula milk or juice. Serum cortisol measurements were performed at pre-dose, 60- and 240-minutes post-dose. In addition, three additional samples were drawn for population PK analyses in subjects between 2 and 6 years i.e. Cohort 1 (N=12). For this purpose, four different sampling schedules with three subjects each were generated, each defining the timepoints after dosing of three additional samples including times at 30-, 45-, 90-, 120-, 150-, 180-, and 300 to 480-minutes post dose (see Table 7).

Medical officer's comment-Dose selection was appropriate. The choice of population PK was acceptable to limit the need for blood sampling in these young children.

Table 7. Additional Sampling Time Points in Cohort 1 for Population PK in Infacort 003

Subject ID number	Sampling timepoints (time sampling window) [min post-dose]						
	30 mins (25-35 min)	45 mins (40-50 min)	90 mins (80-100 min)	120 mins (110-130 min)	150 mins (140-160 min)	180 mins (170-190 min)	*t_{min} (300-480 min)
(b) (6)	X		X				X
	X		X				X
	X		X				X
		X		X			X
		X		X			X
		X		X			X
			X		X		X
			X		X		X
			X		X		X
				X		X	X
				X		X	X
				X		X	X

*t_{min}: last possible sampling timepoint when minimum concentration may be observed
Source Table 3 Study Infacort 003 Clinical Study Report

After 8 hours subjects were restarted on their regular dose of hydrocortisone tablets. Dosing were dispensed in the study by study personnel, so compliance was not an issue. All data was collected from a single study site in Berlin Germany, (b) (4)

Medical officer's comments-
The sponsor was asked to justify why data from a single study site in Berlin, Germany would be applicable to the diverse US pediatric study population. In their response (see SDN 004, Section 1.11.3, Response to Clinical Question 4), the applicant stated that neonatal screening in Germany is similar to the situation found in the US and that treatment for AI is the same throughout the world regardless of underlying pathology. While CAH is less common in Asians or African Americans than Hispanic or White populations the phenotype of presenting symptoms is the same.

Given that there is no reason to suspect bioavailability of Hydrocortisone granules to be different between the US and German populations and that this is a product that is dosed based on clinical response, this medical reviewer considers the foreign data to be adequate for approval in the US.

Schedule of Study Assessments

Table 8. Schedule of Study Assessments for Study Infacort 003

	VISIT 1 SCREENING	VISIT 2 TREATMENT DAY	VISIT 3 FOLLOW-UP	VISIT 4 FOLLOW-UP TELEPHONE CALL
	Day -28/Day -14 to Day -1	Day 1	Day 2, Day 3 or Day 4	Day 8 to Day 11
Written informed consent	X			
Medical history/current medical status	X	X[1]		
Race/ethnicity	X			
Physical examination	X	X[2]	X[2]	
Height/length	X			
Weight	X	X[3]		
Body mass index (derived)	X			
Vital signs	X[4]	X[4]	X[4]	
Inclusion/exclusion criteria	X	X		
Previous and concomitant medication	X	X	X	X
Infacort® administration		X[5]		
Record of entire/incomplete dosing		X		
Palatability assessment		X[6]		
Record of meal content and time ingested		X		
Adverse events		X[7]	X[7]	X[7]
Blood sampling (Cortisol PK, safety cortisol, albumin, CBG)		X[8]		
Blood spot sampling		X[9]		
Blood sampling (population PK)		X[10]		
Admit to clinical centre		X		
Discharge from clinical centre		X		
General assessment			X	
End of study information			X	

1. Concurrent diseases were recorded until the intake of Infacort®.
2. Screening, pre-dose and prior to discharge (abbreviated) on Day 1, Visit 3 where necessary.
3. Cohort 3 only on Day 1.
4. Blood pressure (where possible), pulse and temperature at screening, pre-dose, 60 minutes and prior to discharge on Day 1 and at Visit 3. Additional temperature measurement at 240 minutes on Day 1.
5. Administration approximately 8 hours following prior hydrocortisone dose. Dosing was to take place after a fast of at least 2 hours (45 minutes below 1 year of age). Subjects were not to eat until after the sampling at 60 minutes (30 minutes below 1 year of age).
6. Palatability of Infacort® was assessed after dosing.
7. AEs were recorded from the time of the first intake of Infacort® until Visit 4.
8. Cohorts 1 to 3: Baseline (all study and safety samples), 60 minutes (safety cortisol and PK cortisol only), 240 minutes (PK cortisol only).
9. Cohort 1: Baseline, 60 minutes, 240 minutes and at the 3 population PK timepoints; Cohorts 2 and 3: Baseline, 60 minutes and 240 minutes.
10. Cohort 1 only: Population PK (3 timepoints, post-dose to +8 hours).

Data Source Table 1 Infacort 003 Clinical Study Report

Study Endpoints

Primary endpoint
Maximum serum cortisol concentration with samples taken at baseline, 60 and 240 minutes after dosing

Secondary endpoints
- Serum cortisol concentration up to 6 hours after dosing
- Palatability
- PK parameters estimated in the population PK analysis

Safety endpoints
- Adverse events
- Vital signs

Statistical Analysis Plan

The study size was based on PK data from the Phase 1 studies. Maximum serum cortisol concentration was calculated and presented (sample size, arithmetic mean, geometric mean, SD, coefficient of variation [CV], minimum, median and maximum).

Hypothesis testing was set up to determine if maximum cortisol levels at up to 240 minutes after dosing with Hydrocortisone granules was higher than at baseline using a sign test with a significance level of 1%. The test statistic was based on the difference between the maximum concentration obtained at up to 240 minutes post dose and the baseline pre-dose concentration. The p-value and the number and percent of subjects with an increase in cortisol levels were presented for the primary analysis.

Protocol Amendments

Version 1.0 dated 31 October 2014
- Amended to include IEC comments

Version 2.0 dated 18 December 2014
- Children age 3 to 6 were to be informed about involvement in the study in the presence of caretakers.
- Emla cream was included to minimize pain from IV insertion

Amendment 1 (including but not limited to-)
Version 3.0 dated 06 July 2015

- The study center was finding it difficult to administer the granules using a spoon so the protocol was amended to allow the granules to be administered directly onto the top and towards the back of the child's tongue and washed down immediately with fluid.
- Subject consent form was amended to include birth date
- Samples could be stored at -20C for up to 48 hours prior to transfer to -70C freezer.

Version 4.0 dated 06 August 2015

- Direct venous blood sampling was permitted if the child was too small to insert an IV canula

Amendment 2 (including but not limited to-)
Version 5.0 dated 03 February 2016

- Protocol primary endpoint amended to refer to serum cortisol instead of plasma cortisol
- CRF was amended so that the dates and times of all the doses of hydrocortisone given the previous day were to be collected consistently on the hydrocortisone dosing page and not just the last late evening dose
- CRF was amended to include volume of blood collected

Medical officer's comments-
The difficulty in using a spoon to dose material in certain children will need to be addressed in labeling.

6.2.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with International Council for Harmonization (ICH) Good Clinical Practice (GCP), including the archiving of essential documents according to the applicant.

Financial Disclosure

No investigators in the bioequivalence study Infacort 007 received financial support. This is the main study supporting approval of the indication. In Infacort studies 003 and 004, (b) (6) The sponsor was asked to address these concerns and responded in submission SDN 004. The applicant responded with the following comment:

> The study site personnel saw the patients as per protocol and recorded data pertaining to the study and general health in the medical records. Data was then entered into the

study CRF, the study data was then reviewed by a monitor, with 100% source data verification being conducted. The Sponsor as part of study oversight conducted regular oversite visits to the site, many of which included co-monitoring.

Additionally, the study database was subject to audit in September 2018 and the Clinical Study Report was audited December 2018. No critical findings were identified in these audits. This provides oversight and reassurance in the data.

Since studies Infacort 003 and 004 are only supportive of efficacy they would not be necessary to support the indication, so these reports of financial interest would not affect final approval of the indication.

Patient Disposition

All 24 patients that were screened, were dosed and included in the study results.

Table 9 Subject Disposition in Study Infacort 003

	Cohort 1[1]	Cohort 2[1]	Cohort 3[1]	Overall
	N=12	N=6	N=6	N=24
Disposition	Number of subjects (% of subjects in Cohort)			
Screened	12	6	6	24 (100.0)
Screen failures	0	0	0	0
Eligible subjects not treated	0	0	0	0
Dosed	12	6	6	24
Completed study	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
Early study termination	0	0	0	0

[1] Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days

Data Source Table 4 Infacort 003 Clinical Study Report

Protocol Violations/Deviations

There were no major protocol deviations. One subject in Cohort 1 (Subject (b) (6)) did not have a population PK sample obtained. And one subject in Cohort 2 (Subject (b) (6)) did not have enough blood collected at the 240-minute timepoint to perform the cortisol measurement. Minor protocol deviations seen in two or more patients included: missed vital signs measurements (pulse n=7, BP n=5, and temp n=1), inadequate completion of questionnaires (n=4), need to do venipuncture for blood draw because not possible to insert IV (n=3), and subjects did not remain for the full 6 hours post dosing in the study center (n=2).

Medical officer's comments-
Missing one population PK sample and one 240-minute timepoint was unlikely to affect the study results. The minor protocol deviations were similarly unlikely to affect the study results.

Table of Baseline Demographic Characteristics

Table 10 Baseline Demographic Characteristics in Study Infacort 003

Variable	Cohort 1[1] N=12	Cohort 2[1] N=6	Cohort 3[1] N=6	Overall N=24
Age (days)				
Mean (SD)	1201.7 (344.59)	447.0 (215.63)	22.2 (3.43)	718.1 (578.29)
Median	1197.0	496.5	23.0	704.0
Range	744 to 1708	124 to 664	16 to 26	16 to 1708
Sex, n (%)				
Female	5 (41.7)	2 (33.3)	4 (66.7)	11 (45.8)
Male	7 (58.3)	4 (66.7)	2 (33.3)	13 (54.2)
Ethnicity, n (%)				
Not Hispanic or Latino	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
Ethnic origin, n (%)				
White	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
Body mass index (kg/m^2)				
Mean (SD)	17.42 (1.672)	17.68 (1.547)	12.74 (1.767)	16.32 (2.645)
Median	17.39	17.26	12.29	16.59
Range	14.6 to 20.6	16.4 to 20.5	11.0 to 15.1	11.0 to 20.6
Body surface area (m^2)				
Mean (SD)	0.638 (0.0799)	0.444 (0.0790)	0.222 (0.0315)	0.486 (0.1878)
Median	0.636	0.486	0.223	0.512
Range	0.52 to 0.78	0.32 to 0.51	0.19 to 0.26	0.19 to 0.78

[1] Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days
SD=standard deviation

Source Table 6 Infacort 003 Clinical Study Report

A total of 24 subjects were screened, enrolled and treated in this study. The median ages of subjects were:

- Cohort 1 (age 2 years to <6 years)- 1197 days (3 years, 3 months)
- Cohort 2 (age 28 days to <2 years)- 497 days (1 year and 4 months)
- Cohort 3 (age <28 days)- 23 days.

Subjects were 54% male, and 46% female:

- Cohort 1 (7 male, 5 female)
- Cohort 2 (4 male, 2 female)
- Cohort 3 (2 male, 4 female)

All subjects were Caucasian which reflects the predominant ethnicity of the patient population attending the study center in Berlin, German.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

23/24=96% of subjects were diagnosed with CAH. One subject in Cohort 2 had hypopituitarism (Subject (b) (6).

Table 11 Concurrent Medical Conditions in Study Infacort 003

System Organ Class Preferred Term	Cohort 1[1] N=12	Cohort 2[1] N=6	Cohort 3[1] N=6	Overall N=24
	Number of subjects (% of subjects in Cohort)			
Endocrine disorders	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
Adrenal insufficiency	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
Virilism	1 (8.3)	0	4 (66.7)	5 (20.8)
Hypothyroidism	0	1 (16.7)	0	1 (4.2)
Infections and infestations	1 (8.3)	1 (16.7)	0	2 (8.3)
Rhinitis	0	1 (16.7)	0	1 (4.2)
Skin infection	1 (8.3)	0	0	1 (4.2)
Congenital, familial and genetic disorders	0	0	1 (16.7)	1 (4.2)
Renal hypoplasia	0	0	1 (16.7)	1 (4.2)
Skin and subcutaneous tissue disorders	1 (8.3)	0	0	1 (4.2)
Dermatitis atopic	1 (8.3)	0	0	1 (4.2)

[1] Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days

Source Table 8 Infacort 003 Clinical Study Report

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects were compliant and received the full dose of medication at the study visit.
All of the subjects were taking hydrocortisone, 23 subjects (95.8%) were taking fludrocortisone and 1 subject (4.2%) was taking thyroid therapy (Subject (b) (6) who also had hypothyroidism).

Efficacy Results – Primary Endpoint

The primary endpoint was the maximum serum cortisol level, from one of two measurements taken at 60- and 240-minutes post dose would be statistically significantly greater than baseline. In this study the maximum cortisol level in all 24 subjects occurred at the 60-minute post dose measurement. When analyzed by Cohort, all 12 subjects in Cohort 1 (age 2 to < 6yrs) had cortisol levels above baseline at both 60 minutes and 240 minutes. While all subjects in Cohorts 2 (age 28 days to < 2yrs) and 3 (age < 28days), had cortisol levels higher than baseline at the 60-minute time point, only 2/5 subjects in Cohort 2 and 5/6 subjects in Cohort 3 had cortisol levels above baseline at 240 minutes.

Table 12. Primary Endpoint- Percent of Subjects with Cortisol Levels Above Baseline at 60- and 240- Minutes by Age Cohort (PK population)

	Cohort 1[1]	Cohort 2[1]	Cohort 3[1]	Overall
	N=12	N=6	N=6	N=24
Time	Number of subjects (% of subjects in Cohort with non-missing values)			
C_{max}	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
	p=0.0005	p=0.0313	p=0.0313	p<0.0001
60 minutes	12 (100.0)	6 (100.0)	6 (100.0)	24 (100.0)
	p=0.0005	p=0.0313	p=0.0313	p<0.0001
240 minutes	12 (100.0)	2 (40.0)[2]	5 (83.3)	19 (82.6)[3]
	p=0.0005	p=1.0000	p=0.2188	p=0.0026

[1] Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days
[2] n=5; Subject (b) (6) (Cohort 2) had no result at 240 minutes.
[3] n=23; Subject (b) (6) (Cohort 2) had no result at 240 minutes.
Note: Below the limit of quantification was set to the lower limit of quantification (i.e. 14.10 nmol/L, 5.11 ng/mL) for baseline samples and zero for post-baseline samples.
Data source: Section 14, Table 14.2.7.2
Source Table 11 Infacort 003 Study Report

The overall median increase from baseline in cortisol values measured at C_{max} was 535 nmol/L (19mcg/dL) with a range of 346 (12.5mcg/dL) to 1445 nmol/L (52mcg/dL) at 60 minutes post dose. For comparison a normal reference range for serum cortisol in healthy children 1 to 16 years of age would be highest in the early morning between 3-21mcg/dL at 8AM and somewhat lower in the afternoon between 3-10mcg/dL at 4PM[9].

[9] https://www.ebmconsult.com/articles/lab-test-cortisol-level

Figure 2 Distribution of Cortisol Concentration (nmol/L) at Baseline, and 60- and 240-Minutes Post Dose (PK Population)

Source NDA 213876 SDN 001 Section 5.3.5.2 Infacort 003 ADPC dataset AVAL by ATPT subgroup=Baseline, 60min and 240min

Medical officer's comments-

At the preIND meeting the Agency advised the sponsor not to use "maximum levels of serum cortisol concentration after intake of study drug…" as the primary endpoint for their proposed pivotal study, Infacort 003, and instead recommended that the pivotal study include PK endpoints of AUC, C_{max}, and C_{trough} for cortisol and any other clinically relevant parameters the sponsor may choose to use. However, the applicant chose not to perform the number of pediatric blood samples that would have been required to get enough PK data to evaluate these endpoints in pediatric patients in study Infacort 003 and instead performed the PK endpoint measurements and analysis in the bioequivalence study, Infacort 007, in healthy adults.

Data Quality and Integrity

The data was reviewed by OCS as part of the CoreDF Service to support data quality assessment and the data was found to be of good quality and integrity for review.

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints-

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

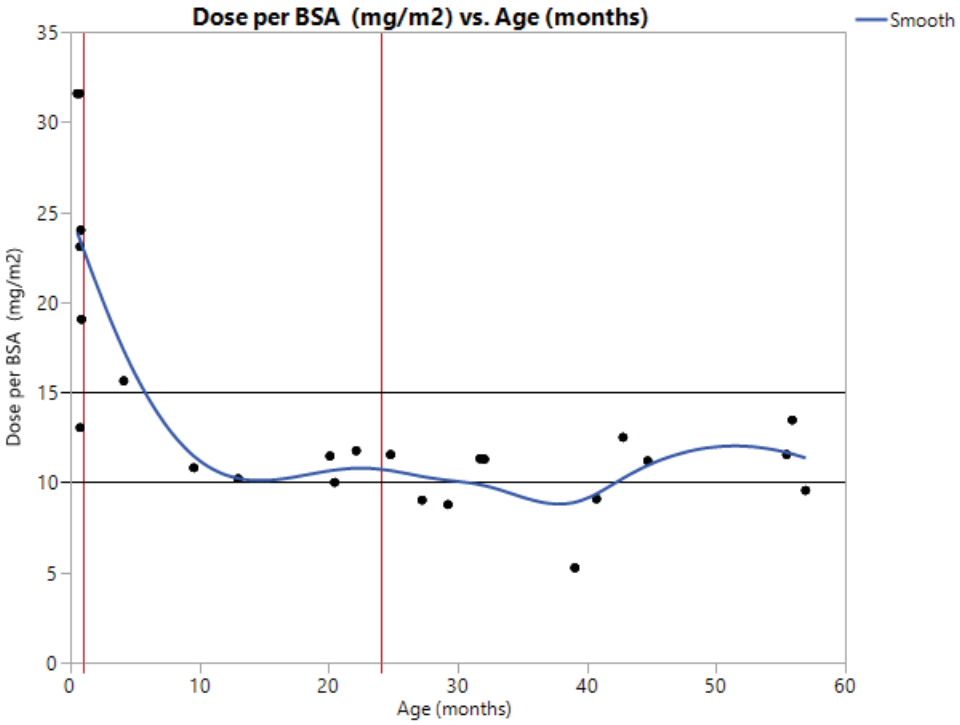
92% of subjects (22/24) had serum cortisol levels <50 nmol/L (1.8 mcg/dL) at baseline. One subject (4%) had a baseline serum cortisol level in the 50 to <100 nmol/L (1.8-3.6 mcg/dL) range and one subject (4%) had a baseline serum cortisol level in the 100 to <150 nmol/L (3.6-5.4 mcg/dL) range. At Cmax (60 minutes post dose), serum cortisol levels were ≥150 nmol/L (5.4 mcg/dL) in all 24 subjects. At 240 minutes post dose, of the 23 subjects with results, 10 subjects (44%) had serum cortisol levels <50 nmol/L, 10 subjects (44%) had levels of 50 to <100 nmol/L, 1 subject (4%) had a level of 100 to <150 nmol/L, and 2 subjects (9%) had serum cortisol levels ≥150 nmol/L (see Fig. 2 above).

> *Medical officer's comments-*
> *It was noted that some of the reported serum cortisol levels were well above the laboratory normal reference range, 3-21mcg/dL, as referenced above for healthy children. A review of these data by this medical reviewer identified that all the very high values of serum cortisol i.e. > 800nmol/L (29md/dL) occurred in Cohort 3, children less than 28 days of age. At first this medical reviewer was concerned that children under one month of age might be poor metabolizers which might have caused the higher than expected drug levels. So, the applicant was asked to supply total daily dosing information for all children in this study (see SDN0013). A review of the total daily dosing information showed that these neonates (< 28 days of age) were intentionally prescribed higher doses with a median dose of 23mg/m^2/day and a range of 13 to 32 mg/m^2/day compared to older children over 1 month of age who received a median dose of 11mg/m^2/day and a range of 5 to 15.6mg/m^2/day. These average doses were nearly double the recommended starting doses of 10 to 15mg/m^2/day in children with CAH that the applicant is proposing. However, there is precedent in the literature for higher doses up to 30mg/m^2/day[10] to deal with hypoglycemia and markedly elevated adrenal sex hormones in newborn infants, and when asked about this the applicant stated that "The doses given to the neonatal subjects are higher reflecting the need to gain control of the*

[10] Up to Date- **Treatment of classic congenital adrenal hyperplasia sue to 21-hydorxylase deficiency in infants and children** Merke DP Literature through July 2020 updated July 28, 2020

hypothalamo-pituitary-adrenal axis that had not been controlled during fetal life and are consistent with Endocrine Society guidelines … reflecting medical practice to treat very young infants with a higher dose initially." Note all but one patient over 1 month of age were within or below the proposed starting dose Endocrine Society guidelines for children with CAH[4], i.e. between 10 and 15mg/m^2/day (see horizontal lines in Figure 3 below).

Figure 3 Daily Hydrocortisone Dosing for Subjects in Infacort 003 by Age (months) and Body Surface Area (mg/m^2)



Source NDA 213876 SDN 001 Section 5.3.5.2 Infacort 003 ADPC dataset and SDN 0013 (clinical-info-amend-responsose-rfi-24july)

2) Palatability of the investigational product

Parent's or caretaker's questionnaires:
83% (19/23) of parents or caretakers who completed the palatability questionnaire agreed or strongly agreed that their child found swallowing easy.

My child found swallowing easy	
Agree	10
Strongly Agree	9
Disagree	3

Neither Agree nor Disagree	1
No Response	1

65% (15/23) agreed or strongly agreed that their child showed a positive reaction after Hydrocortisone granules was given.

My child showed a positive reaction after Infacort was given	
Agree	8
Strongly Agree	7
Neither Agree nor Disagree	6
Disagree	2
No Response	1

96% (21/22) would be happy to give their child Hydrocortisone granules in the future, and

I would be happy to give my child Infacort in the future	
Agree	8
Strongly Agree	13
Neither Agree nor Disagree	1
No Response	2

96% (21/22) preferred it to their usual hydrocortisone medication.

Overall, I would prefer Infacort for my child over the usual Hydrocortisone medication	
Strongly Agree	14
Agree	7
Disagree	0
Neither Agree nor Disagree	1
No Response	2

Children (Cohort 1) questionnaire:
100% (6/6) of the children felt the medicine was very good or not bad to taste.

What did the medicine taste like?	
Not done	18
Very Good	3
Not good/bad	3
Very Bad	0

83% (5/6) of the children felt the medicine was very good or not bad to take again.

Would you take the medicine again?	
Not done	18
Very Good	4
Not good/bad	1
Very Bad	1

67% (4/6) of the children felt the medicine was very good or not bad to swallow.

What was it like to swallow the medicine?	
Not done	18
Very Good	3
Not good/bad	1
Very Bad	2

Medical officer's comments-
In general, the questionnaire comments support the palatability of Hydrocortisone granules. But there was no control group here for comparison, and only a small number of children, primarily those in cohort 1, 6/24=25% directly responded to the children's questionnaire. Off not,e a small but substantial 17 to 33% of the respondents did not like taking the medicine.

Note, in study Infacort 004 four of the subjects (22%) withdrew from the study as they preferred the taste or texture of a pharmacy compounded preparation. And the study was amended to allow for sprinkling of the formulation onto yogurt, or apple sauce or to permit direct administration on the back of the tongue followed by subsequent washing down with water, breast milk of apple juice to facilitate administration, suggesting that palatability was still an issue for some children.

Dose/Dose Response

Not applicable as this was a single dose study. The dose given was the same as the subject's usual immediate release hydrocortisone dose given at the same time the previous day.

Durability of Response

Not applicable. Durability of response beyond the single initial treatment was not studied.

Persistence of Effect

The median terminal half-life of Hydrocortisone granules is about one and a half hours but can range from 1 to 4 hours (See Infacort 007). At 240 minutes post dose, 10 of the 23 subjects (44%) had serum cortisol levels <50 nmol/L, 10 of 3 subjects (44%) had levels of 50 to <100 nmol/L, 1 subject (4%) had a level of 100 to <150 nmol/L, and 2 subjects (9%) had serum cortisol levels ≥150 nmol/L (see Fig. 2 above).

Additional Analyses Conducted on the Individual Trial

None

6.3. **Study Infacort 004**-A PHASE 3 OPEN-LABEL STUDY OF INFACORT IN NEONATES, INFANTS AND CHILDREN LESS THAN 6 YEARS OF AGE WITH ADRENAL INSUFFICIENCY

6.3.1. Study Design

Overview and Objective

Study Infacort 004 was designed as an open-label, long term, safety extension study of Hydrocortisone granules in subjects who completed Infacort 003.

Trial Design Infacort 004

Infacort 004 was an open-label, non-randomized, follow up study of subjects from Infacort 003. All 24 subjects who completed study Infacort 003 were offered the opportunity to participate but only 18 elected to enroll and were treated. Subjects were to receive their usual clinically appropriate dose of hydrocortisone as Hydrocortisone granules as determined by the Study Investigator. All subjects were dosed three times a day (TID). Subjects typically received either the same dose TID or received higher doses with the morning and evening doses, and lower doses in the afternoon. After an initial visit, subjects attended monthly visits for the first 2 months, and then continued with visits every 3 months. Subjects were to be treated in this study until they met the study withdrawal criteria, they decided to discontinue the study or until Hydrocortisone granules became commercially available.

A total of 6 subjects withdrew early, all due to "Withdrawal of Consent". One subject spat out the first dose and was withdrawn from the study without any further dosing, and the remaining 5 subjects were withdrawn due to issues with having to give the last dose late at night. The study was stopped when Hydrocortisone granules became commercially available in Germany in February 2018.

Medical officer's comment- While the applicant is proposing dosing three or four times a day in the package insert, it is interesting that all subjects in this study were dosed three

times a day and that 5 out of the 18 patients withdrew because of the need to give the last dose late at night on a strict 8-hour schedule. Therefore, expecting dosing four times daily which could require the child being woken up multiple times in the middle of the night could be problematic. When asked why they were recommending four times a day dosing the sponsor mentioned that some physicians found it helpful "in selected patients as it appears to more closely mimic the circadian rhythm of cortisol" (see SDN 014). That said one of the references supplied by the applicant, Whitaker et al. 2015[11], which surveyed 67 pediatric endocrinologists from 16 countries, identified thrice daily dosing as most common at 94%, followed by once, twice and four times daily dosing, each at 2%. Clearly, the vast majority of pediatric endocrinologists appear to recommend thrice daily dosing.

Inclusion Criteria-including but not limited to:

- Same as for Infacort 003 (see Section 6.1.1)
- Successful completion of study Infacort 003

Exclusion Criteria-including but not limited to:

- Same as for Infacort 003 (see Section 6.1.1)

Medical officer's comment-The inclusion/exclusion criteria were appropriate.

[11] Whitaker MJ, Spielmann S, Digweed D, et al. **Development and testing in healthy adults of oral hydrocortisone granules with taste masking for the treatment of neonates and infants with adrenal insufficiency.** J Clin Endocrinol Metab. 2015;100:1681-1688.

Schedule of Study Assessments

Table 13. Schedule of Study Assessments for Study Infacort 004

	Initial Visit	Interim Visits[1]	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 and 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
AEs and SAEs[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 was provided at least 24 hours prior to enrolment
3. Medical history from Infacort 003 was used, plus any changes since the subject was enrolled in the Infacort 003 study
4. Blood pressure (where possible), heart rate and temperature
5. Included 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 were recorded from the time of the first intake of Infacort® in this study until the final visit. SAEs were 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 were reported only if the Investigator suspected 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 were recorded
9. The time of blood sampling was noted, as well as the time and dose of the previous administration of glucocorticoid. Where possible the blood spot sample was 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 withdrawal from the study

Data Source Table 1 Infacort 004 Clinical Study Report

Study Endpoints

Primary endpoint
The primary endpoint was the nature and occurrence of serious adverse events and adverse events observed throughout the study.

Secondary endpoints
- SDS for height and weight
- cortisol (all subjects)
- adrenal androgen levels (17-OHP, androstenedione, testosterone) from dried blood

spot samples in CAH subjects only
- Tanner Development Stage

Additional safety endpoints
- Adverse events
- Vital signs

Statistical Analysis Plan

Only descriptive statistical methods were used in the analyses of the data. All recorded and derived variables were to be presented using appropriate descriptive summary tables (continuous data: sample size, mean, standard deviation [SD], minimum, median, maximum; categorical data: sample size, absolute and relative frequency). Changes over time of continuous and categorical data were analyzed by presenting summary statistics for the actual values and changes from baseline at each visit, if appropriate.

Protocol Amendments

Version 1.0 dated 23 July 2015
- Original protocol

Version 2.0 dated 15 Sept 2015 (including but not limited to:)
- Early withdrawal criterion was expanded to include:
  - Any condition which could impair the subject's ability to swallow.
  - Three or more sick day rules without a reasonable explanation such as infection, fever, trauma etc.
  - Two or more episodes of Addisonian crisis without a reasonable explanation such as infection, fever, trauma etc.

Version 3.0 dated 25 July 2016-Amendment 1 (including but not limited to:)
- In addition to the Hydrocortisone granules being administered directly onto the top and towards the back of the child's tongue, it was added that the granules could also be mixed with yoghurt, fruit purees (e.g., apple sauce) or fruit mousses immediately before being administered to the child. The granules could also be washed down with water, breast milk, formula milk or whole milk following administration.

Version 4.0 dated 20 July 2017-Amendment 2 (including but not limited to:)
- AEs of special interest AESIs were changed to include:

- all AEs that led to sick day rules or use of sick day medication whether serious or not
- any AE that led to medical intervention at a hospital or clinic visit
- any occurrence of adrenal crisis

- It was discovered that no mean and standard deviation for the age- and gender-matched German reference population was available for growth velocity. 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.

6.3.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with International Council for Harmonization Good Clinical Practice, including the archiving of essential documents according to the applicant.

Financial Disclosure

Financial disclosure was the same for Infacort 003 and Infacort 004. Refer to the financial disclosure assessment previously discussed under Section 6.2.2.

Patient Disposition

Out of the 24 subjects who completed study Infacort 003, 18 subjects were enrolled in the Infacort 004 extension study. Of the six subjects who did not want to reenroll in the study four were because the parents did not want to make frequent visits to the study site, one because of concerns about loss of disease control, and one because the child vomited during the Infacort 003 study so the mother did not want the child to take part in the follow up study according to a personal communication from the Investigator.

Of the 18 subjects enrolled in the study, one subject (Subject (b) (6)) refused to take the first dose and was withdrawn from the study without treatment. It was noted that this child had an ongoing problem of refusing taking medications. A year later the parents asked to reenroll this child due to problems with pharmacy constituted capsules, and he was treated for the final 17 months of the study without any further problems. During the study an additional five subjects (Subjects (b) (6)) withdrew consent and were withdrawn after 17, 4, 150, 1, and 31 days, respectively. In all of these cases the children were withdrawn because the parents did not want the children woken up at night to administer the third daily dose using a

strict 8-hour regimen. In four of these cases the child mentioned a preference for a sweeter or more palatable pharmacy compounded formulation which may have contributed to study withdrawal.

Protocol Violations/Deviations

No major protocol deviations were reported. 17 of the 18 subjects had at least one minor protocol deviation. The most common deviations related to incomplete administration of the study medication (n=16) and issues with blood sampling and testing (n=12). For most subjects incomplete dosing was reported for a small number of occasions typically less than three, except for Subject (b) (6) who had >20 doses of Hydrocortisone granules not taken as prescribed throughout the study (i.e. received < 75% of the dose), see Treatment Compliance below.

Table of Demographic Characteristics

Table 14 Baseline Demographic Characteristics in Study Infacort 004

Variable	Cohort 1[1] N=9	Cohort 2[1] N=6	Cohort 3[1] N=3	Overall N=18
Age (days)				
Mean (SD)	1546.4 (388.34)	707.2 (214.72)	75.7 (60.25)	1021.6 (650.84)
Median	1316.0	747.5	46.0	1000.0
Range	1077 to 2084	394 to 923	36 to 145	36 to 2084
Sex, n (%)				
Female	4 (44.4)	2 (33.3)	2 (66.7)	8 (44.4)
Male	5 (55.6)	4 (66.7)	1 (33.3)	10 (55.6)
Ethnicity, n (%)				
Not Hispanic or Latino	9 (100.0)	6 (100.0)	3 (100.0)	18 (100.0)
Ethnic origin, n (%)				
White (Caucasian)	9 (100.0)	6 (100.0)	3 (100.0)	18 (100.0)
BMI (kg/m^2)				
Mean (SD)	17.01 (2.356)	17.85 (1.384)	15.35 (1.909)	17.02 (2.083)
Median	16.42	17.53	16.00	16.83
Range	13.7 to 22.1	16.4 to 20.1	13.2 to 16.8	13.2 to 22.1
BSA (m^2)				
Mean (SD)	0.716 (0.0809)	0.536 (0.0679)	0.269 (0.0648)	0.582 (0.1803)
Median	0.708	0.563	0.271	0.594
Range	0.58 to 0.84	0.44 to 0.60	0.20 to 0.33	0.20 to 0.84

[1] Infacort 003 Cohorts: Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days
BMI=body mass index; BSA=body surface area; SD=standard deviation
BMI was calculated using the following formula: BMI = W / (H*H) where W is weight in kg, and H is height/length in m
BSA was calculated using Du Bois's formula (Du Bois 1989) where W is weight in kg, and H is height in cm
Data source: Section 14, Table 14.1.2.1 and Table 14.1.2.2

Source Table 5 Infacort 004 Clinical Study Report

Of the 18 subjects enrolled and treated in this study. The median ages of subjects by study cohort were:

- Cohort 1 (age 2 years to <6 years in Infacort 003)- 1316 days (3 years, 7 months)
- Cohort 2 (age 28 days to <2 years in Infacort 003)- 747 days (2 years) and
- Cohort 3 (age <28 days in Infacort 003)- 46 days.

Subjects were 56% male, and 44% female:

- Cohort 1 (5 male, 4 female)
- Cohort 2 (4 male, 2 female)
- Cohort 3 (1 male, 2 female)

All subjects were Caucasian.

17/18=94% of subjects were diagnosed with CAH. One subject in Cohort 2 had hypopituitarism (Subject (b) (6) .Approximately half the subjects were male. All of the subjects entered into Study Infacort 004 were white, which reflects the predominant ethnicity of the patient population attending the study center in Berlin, Germany.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 15 Concurrent Medical Conditions in Study Infacort 004

System Organ Class Preferred Term	Cohort 1[1] N=9	Cohort 2[1] N=6	Cohort 3[1] N=3	Overall N=18
	Number of subjects (% of subjects in cohort)			
Endocrine disorders	9 (100.0)	6 (100.0)	3 (100.0)	18 (100.0)
Adrenal insufficiency	9 (100.0)	6 (100.0)	3 (100.0)	18 (100.0)
Virilism	1 (11.1)	0	2 (66.7)	3 (16.7)
Hypothyroidism	0	1 (16.7)	0	1 (5.6)
Skin and subcutaneous tissue disorders	1 (11.1)	1 (16.7)	0	2 (11.1)
Dermatitis atopic	1 (11.1)	0	0	1 (5.6)
Neurodermatitis	0	1 (16.7)	0	1 (5.6)
Infections and infestations	1 (11.1)	1 (16.7)	0	2 (11.1)
Rhinitis	0	1 (16.7)	0	1 (5.6)
Skin infection	1 (11.1)	0	0	1 (5.6)
Congenital, familial and genetic disorders	0	1 (16.7)	1 (33.3)	2 (11.1)
Cryptorchism	0	1 (16.7)	0	1 (5.6)
Renal hypoplasia	0	0	1 (33.3)	1 (5.6)
Gastrointestinal disorders	1 (11.1)	0	0	1 (5.6)
Dental caries	1 (11.1)	0	0	1 (5.6)
Injury, poisoning and procedural complications	1 (11.1)	0	0	1 (5.6)
Scar	1 (11.1)	0	0	1 (5.6)
Metabolism and nutrition disorders	1 (11.1)	0	0	1 (5.6)
Obesity	1 (11.1)	0	0	1 (5.6)
Musculoskeletal and connective tissue disorders	0	1 (16.7)	0	1 (5.6)
Positional plagiocephaly	0	1 (16.7)	0	1 (5.6)

[1] Infacort 003 Cohorts: Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days
MedDRA Version 21.0
Data source: Section 14, Table 14.1.3.2.

Source Table 6 Infacort 004 Clinical Study Report

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance-
Treatment compliance was affected by vomiting/posseting, spillage and "other" which referred to "dose not taken/forgotten, mistake, subject refused to take the dose, subject overslept so dose was missed, only 1 mg given by mistake instead of 2 mg, dose was missed due to blood sampling, and hydrocortisone suppository given instead due to subject vomiting" (see Table 16 below). While between one and nine subjects each month had episodes of underdosing, correct dose administration was still observed at a mean of 93% of treatment days.

Table 16 Problems Resulting in < 75% of Study Drug Administration in Study Infacort 004

Visit	Cohort 1[1] N=9	Cohort 2[1] N=6	Cohort 3[1] N=3	Overall N=18
Reason for reduced drug intake	Number of events/subjects (% of subjects in cohort)			
Visit 1 - Initial Visit				
Vomiting/posseting	0	1/1 (16.7)	0	1/1 (5.6)
Visit 2 - 1st Month				
Vomiting/posseting	0	6/1 (16.7)	2/1 (33.3)	8/2 (11.1)
Spillage	1/1 (11.1)	0	0	1/1 (5.6)
Other	1/1 (11.1)	2/1 (16.7)	0	3/2 (11.1)
Visit 3 - 2nd Month				
Vomiting/posseting	1/1 (11.1)	3/1 (16.7)	1/1 (33.3)	5/3 (16.7)
Spillage	1/1 (11.1)	0	0	1/1 (5.6)
Other	0	1/1 (16.7)	0	1/1 (5.6)
Visit 4 - 5th Month				
Choking	0	2/1 (16.7)	0	2/1 (5.6)
Spillage	1/1 (11.1)	3/2 (33.3)	3/1 (33.3)	7/4 (22.2)
Other	1/1 (11.1)	3/2 (33.3)	4/1 (33.3)	8/4 (22.2)
Visit 5 - 8th Month				
Vomiting/posseting	0	1/1 (16.7)	2/1 (33.3)	3/2 (11.1)
Spillage	2/1 (11.1)	0	1/1 (33.3)	3/2 (11.1)
Other	2/1 (11.1)	1/1 (16.7)	5/1 (33.3)	8/3 (16.7)
Visit 6 - 11th Month				
Vomiting/posseting	8/4 (44.4)	1/1 (16.7)	0	9/5 (27.8)
Spillage	2/1 (11.1)	0	4/1 (33.3)	6/2 (11.1)
Other	0	0	5/1 (33.3)	5/1 (5.6)
Visit 7 - 14th Month				
Vomiting/posseting	1/1 (11.1)	2/1 (16.7)	1/1 (33.3)	4/3 (16.7)
Spillage	0	1/1 (16.7)	2/1 (33.3)	3/2 (11.1)
Other	0	1/1 (16.7)	6/1 (33.3)	7/2 (11.1)
Visit 8 - 17th Month				
Vomiting/posseting	0	0	1/1 (33.3)	1/1 (5.6)
Spillage	0	0	1/1 (33.3)	1/1 (5.6)
Other	0	0	6/1 (33.3)	6/1 (5.6)
Visit 9 - 20th Month				
Vomiting/posseting	1/1 (11.1)	0	0	1/1 (5.6)
Spillage	0	2/2 (33.3)	0	2/2 (11.1)
Other	0	0	13/1 (33.3)	13/1 (5.6)
Visit 10 - 23rd Month				
Other	0	0	12/1 (33.3)	12/1 (5.6)
Final Visit				
Vomiting/posseting	3/1 (11.1)	0	0	3/1 (5.6)
Spillage	0	1/1 (16.7)	0	1/1 (5.6)
Other	1/1 (11.1)	1/1 (16.7)	12/1 (33.3)	14/3 (16.7)

[1] Infacort 003 Cohorts: Cohort 1: 2 years to <6 years; Cohort 2: 28 days to <2 years; Cohort 3: <28 days
'Other' includes dose not taken/forgotten, mistake, subject refused to take the dose, subject overslept so dose was missed, only 1 mg given by mistake instead of 2 mg, dose was missed due to blood sampling, and hydrocortisone suppository given instead of Infacort® due to subject vomiting (Appendix 16.2, Listing 16.2.5.3)
Data source: Section 14, Table 14.1.6.2.
Source Table 9 Infacort 004 Clinical Study Report

Concomitant Medications-
All subjects (100%) were taking hydrocortisone, 17 subjects (94%) all with CAH were taking fludrocortisone, one subject with hypothyroidism (6%) was taking thyroid therapy, and three subjects (17%) were taking Vitamin D at baseline.

The most common concomitant medications during the study were anti-inflammatory and antirheumatic products- ibuprofen 13 subjects (72%), paracetamol 7 subjects (39%) and prednisone 4 subjects (22%).

Rescue Medications-
Thirteen subjects (72%) had required sick day rule implementation during the study. The primary reason was for fever, with 103 episodes in 13 subjects, followed by cases of "other" 47 episodes in 10 subjects, vomiting 14 episodes in 5 subjects and diarrhea 9 episodes in 2 subjects. Six of these events in three subjects were reported as AEs of special interest (AESIs) due to use of sick day medication that led to medical intervention at a hospital/clinic visit. These included Subject (b) (6) with 2 AESIs of pharyngotonsillitis and scarlet fever; Subject (b) (6) with 3 AESIs of obstructive bronchitis, URI with conjunctivitis, and influenza with fever/vomiting/cough; Subject (b) (6) with one AESI of tonsillitis with vomiting. All these events were considered nonserious and not related to Hydrocortisone granules. No cases of adrenal crisis were reported.

Table 17 Reasons for Implementation of Sick Day Rules in Study Infacort 004

Visit	Vomiting	Fever	Diarrhoea	Other	Missing	Any reason
	Number of events/subjects (% of subjects overall)					
Visit 2	0/0 (0.0)	6/5 (27.8)	1/1 (5.6)	1/1 (5.6)	0/0 (0.0)	8/6 (33.3)
Visit 3	1/1 (5.6)	4/3 (16.7)	0/0 (0.0)	3/2 (11.1)	0/0 (0.0)	8/5 (27.8)
Visit 4	3/2 (11.1)	10/6 (33.3)	1/1 (5.6)	1/1 (5.6)	1/1 (5.6)	16/8 (44.4)
Visit 5	3/2 (11.1)	12/7 (38.9)	1/1 (5.6)	8/3 (16.7)	0/0 (0.0)	24/10 (55.6)
Visit 6	1/1 (5.6)	19/8 (44.4)	1/1 (5.6)	7/3 (16.7)	0/0 (0.0)	28/10 (55.6)
Visit 7	2/1 (5.6)	9/6 (33.3)	0/0 (0.0)	5/2 (11.1)	0/0 (0.0)	16/7 (38.9)
Visit 8	0/0 (0.0)	7/4 (22.2)	1/1 (5.6)	6/2 (11.1)	0/0 (0.0)	14/5 (27.8)
Visit 9	1/1 (5.6)	13/5 (27.8)	2/1 (5.6)	7/2 (11.1)	0/0 (0.0)	23/7 (38.9)
Visit 10	1/1 (5.6)	12/6 (33.3)	1/1 (5.6)	6/4 (22.2)	0/0 (0.0)	20/9 (50.0)
Visit 11	1/1 (5.6)	1/1 (5.6)	0/0 (0.0)	1/1 (5.6)	0/0 (0.0)	3/3 (16.7)
Final Visit	1/1 (5.6)	8/6 (33.3)	1/1 (5.6)	2/2 (11.1)	0/0 (0.0)	12/9 (50.0)
Overall	14/5 (27.8)	101/13 (72.2)	9/2 (11.1)	47/10 (55.6)	1/1 (5.6)	172/13 (72.2)

Visit 2 - 1st Month, Visit 3 - 2nd Month, Visit 4 - 5th Month, Visit 5 - 8th Month, Visit 6 - 11th Month,
Visit 7 - 14th Month, Visit 8 - 17th Month, Visit 9 - 20th Month, Visit 10 - 23rd Month, Visit 11 - 26th Month
A category of Missing indicates that a Start/Stop date of event has been recorded, but a reason not provided
Final Visit includes data from all subjects, including those withdrawn early
Data source: Section 14, Table 14.2.7.2.

Source Table 17 Infacort 004 Clinical Study Report

A closer look at the cases of "other" that led to implementation of the sick day rule identified cases of Infections (e.g. URIs, gastroenteritis, pyelonephritis, conjunctivitis, otitis media, scarlet fever, and erysipelas); surgery or dental procedure; injury (e.g. fall with cut on forehead and

jelly fish sting) and stress (e.g. physical-prolonged activity after hiking, headache, stomachache; emotional- nervousness/excitement about starting kindergarten, going away overnight, a birthday party, etc.)

> *Medical officer's comment-Conditions that led to the implementation of sick day rules included infections, surgery, dental procedures, injury and physical and emotional stress all of which are common events in childhood. Without a randomized, blinded control group it is not possible to tell if the event rates were higher than might be expected, but it is this medical reviewer's assessment that from the limited data there does not appear to be clear evidence of the need for excess application of sick-day rules in this study which would have suggested undertreatment.*

Efficacy Results – Primary Endpoint

The study was designed primarily as a safety study. It was not powered to evaluate a specific primary efficacy endpoint. The primary endpoint was nature and occurrence of SAEs and AEs observed throughout the study

See Review of Safety Section 8 below.

Data Quality and Integrity

Data quality of the submitted data was reviewed with the CoreDF service and found to be of adequate quality and integrity.

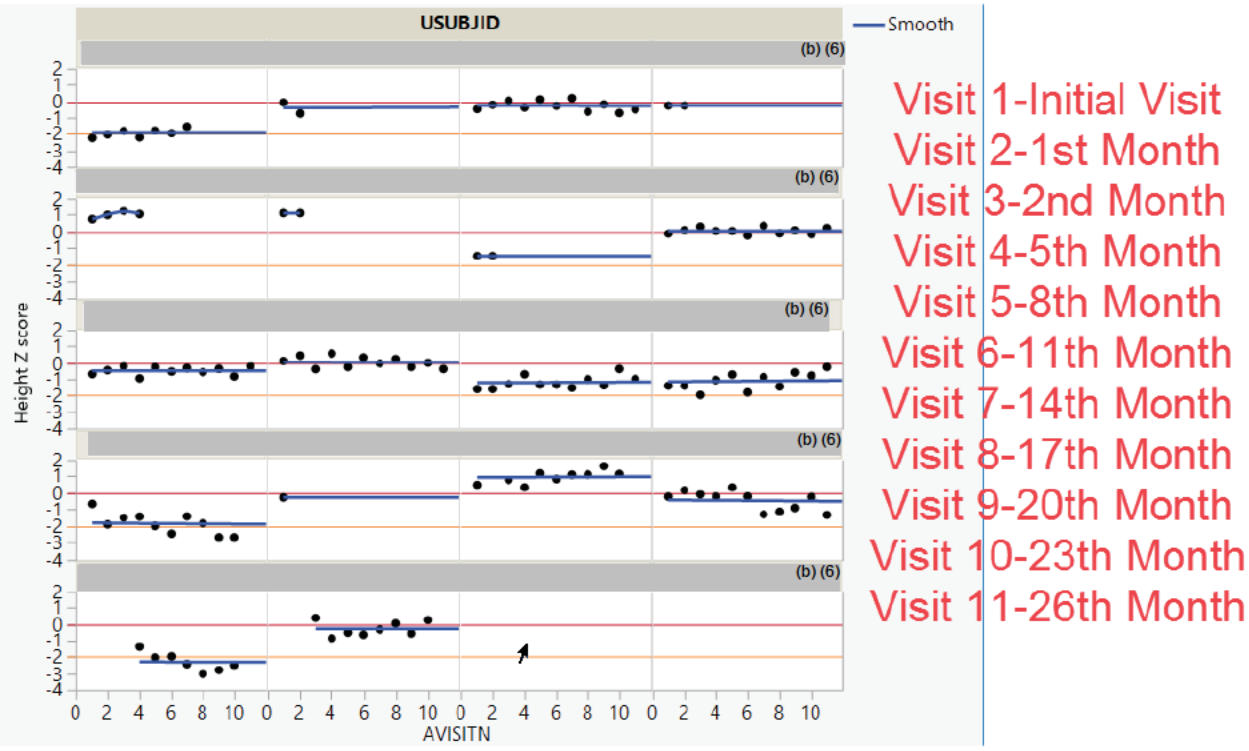
Efficacy Results – Secondary and other relevant endpoints

Standard Deviation Scores (SDS) for height and weight
Underdosing hydrocortisone in patients with AI can lead to weight loss, whereas overdosing can lead to obesity and decreased linear growth. Therefore, height and weight data may be useful measures to monitor during chronic treatment. It is this medical reviewer's assessment that maintaining a stable growth rate would be a measure of drug efficacy. The applicant initially proposed to present growth velocity data as a secondary endpoint but was unable to identity mean and standard deviation growth velocity data for the age- and gender-matched German reference population. Therefore, they chose instead to present height and weight data using SDS scores. SDS scores measure how many standard deviations below or above the population mean a given value is. An SDS score of 0 represents the mean. Clinical concern is typically raised when levels are measured at +2 or -2 Z-scores with respect to the mean. The height Z-score data (see Figure 4) demonstrate that most subjects maintained fairly steady growth patterns

within the +2 and -2 boundaries except for subjects (b) (6) who had low height Z-score levels bordering the -2 line (see orange line). With respect to weight Z-score subjects (b) (6) and (b) (6) had a weight Z-scores above zero representing mean weight for age, whereas subject (b) (6) also had weight Z-scores measured at 2 standard deviations below the mean (see Figure 5). Subject (b) (6) had hypopituitarism and had not yet started on growth hormone treatment according to a personal communication from the investigator to the applicant, which would explain the isolated low height Z-score. Subject (b) (6) had renal hypoplasia, which is often accompanied by growth deficiency according to a personal communication from the investigator to the applicant and would explain the low height and weight Z-scores seen for this subject. No past medical history information was available as to why subject (b) (6) had the low baseline height Z-score. However, she had 3 SAEs of gastroenteritis and 2 SAEs of vomiting during study Infacort 004 which might explain her slight loss in weight Z-score during the study.

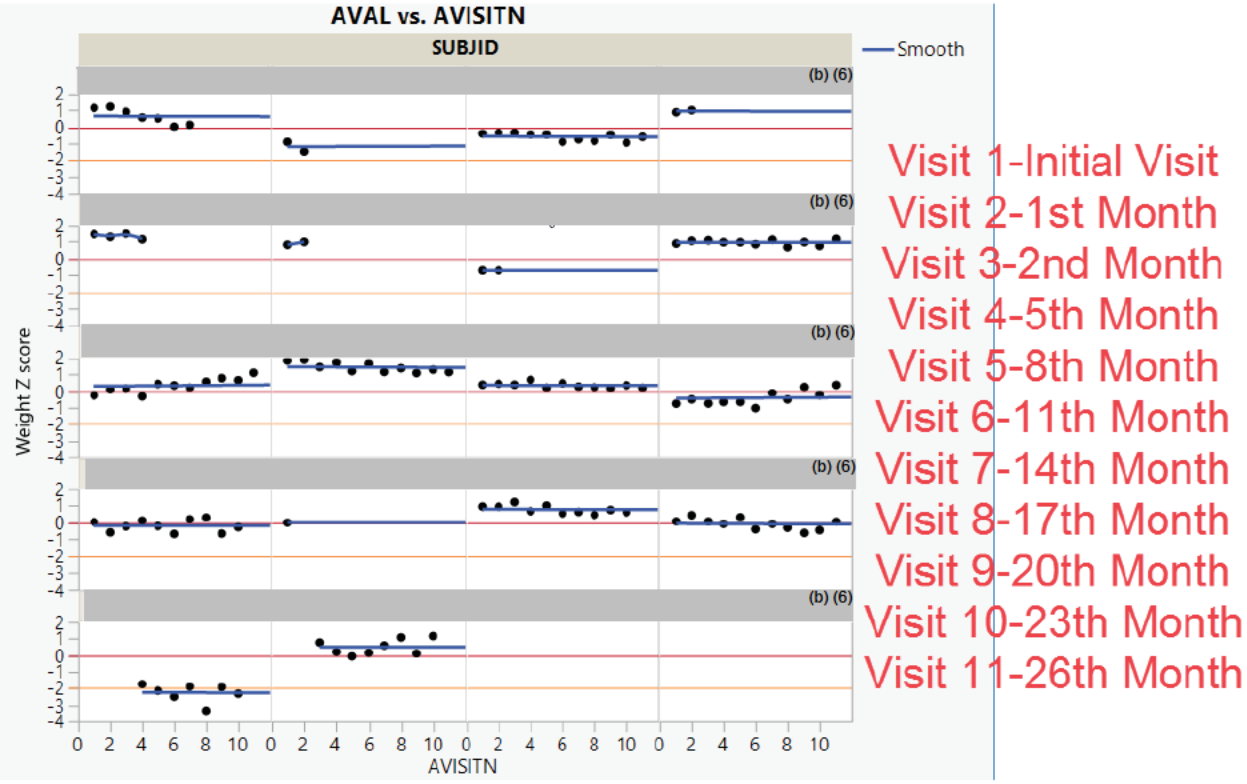
Medical officer's comment- In general, there were no consistent trends suggesting growth acceleration or suppression for most subjects. Demonstration of reasonably steady levels of growth out to visit 11, i.e. month 26, support the efficacy of chronic treatment with Hydrocortisone granules.

Figure 4 Height Z-Score by Study Visit for Each Subject in Study Infacort 004



Study 004 ADVS PARAMCD=HEIGHTZ AVAL vs VISTN, by USUBJID Red line refers to Z-score=0, Orange line refers to Z-score= -2

Figure 5 Weight Z-Score by Study Visit for Each Subject in Study Infacort 004

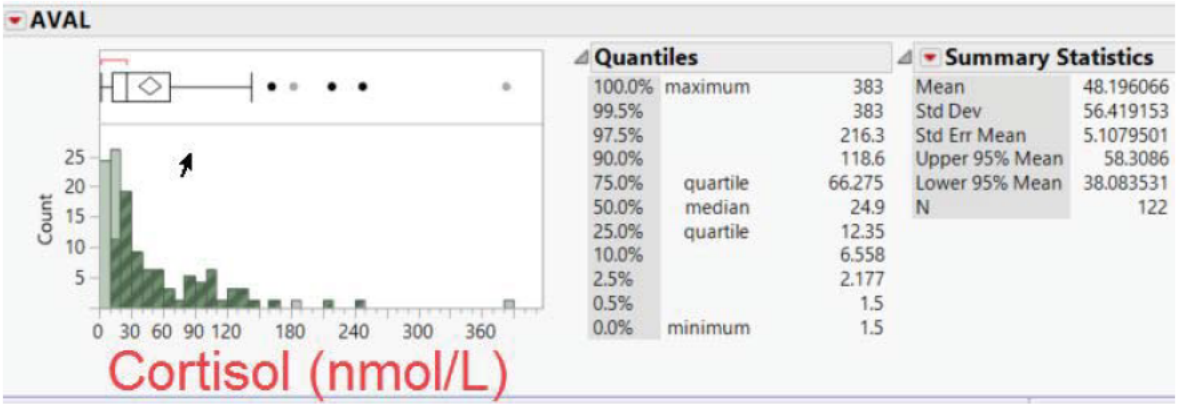


Study 004 ADVS PARAMCD=WEIGHTZ AVAL vs VISTN, by USUBJID Red line refers to Z-score=0, Orange line refers to Z-score= -2

Cortisol (all subjects)

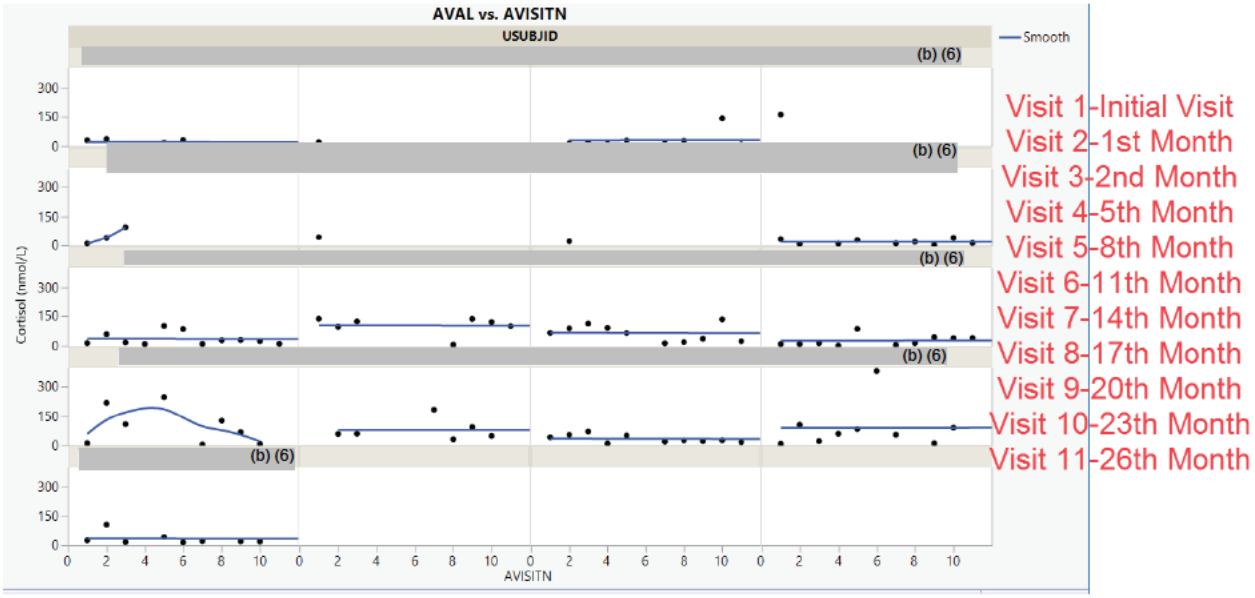
Blood collection points were not timed in Infacort 004, although it was suggested that they be taken in the morning, so the results include the natural daily fluctuations in cortisol levels (see Figure 6.) Even so, 66% of the values were within the normal reference range based on age and gender (see columns with cross hatches in the figure) during treatment with Hydrocortisone granules.

Figure 6 Random Morning Cortisol Measurements in Study Infacort 004



Study 004 ADLB Count of AVAL, for PARAMCD=CORTISOL, Crosshatched columns-> Analysis Reference Range Indicator (ANRIND)=Normal (Normal range for age and gender)

Figure 7 Random Cortisol Levels by Study Visit for Each Subject in Infacort 004



Study 004 ADLB by PARAM=CORTISOL, AVAL vs AVISTN by USUBJID

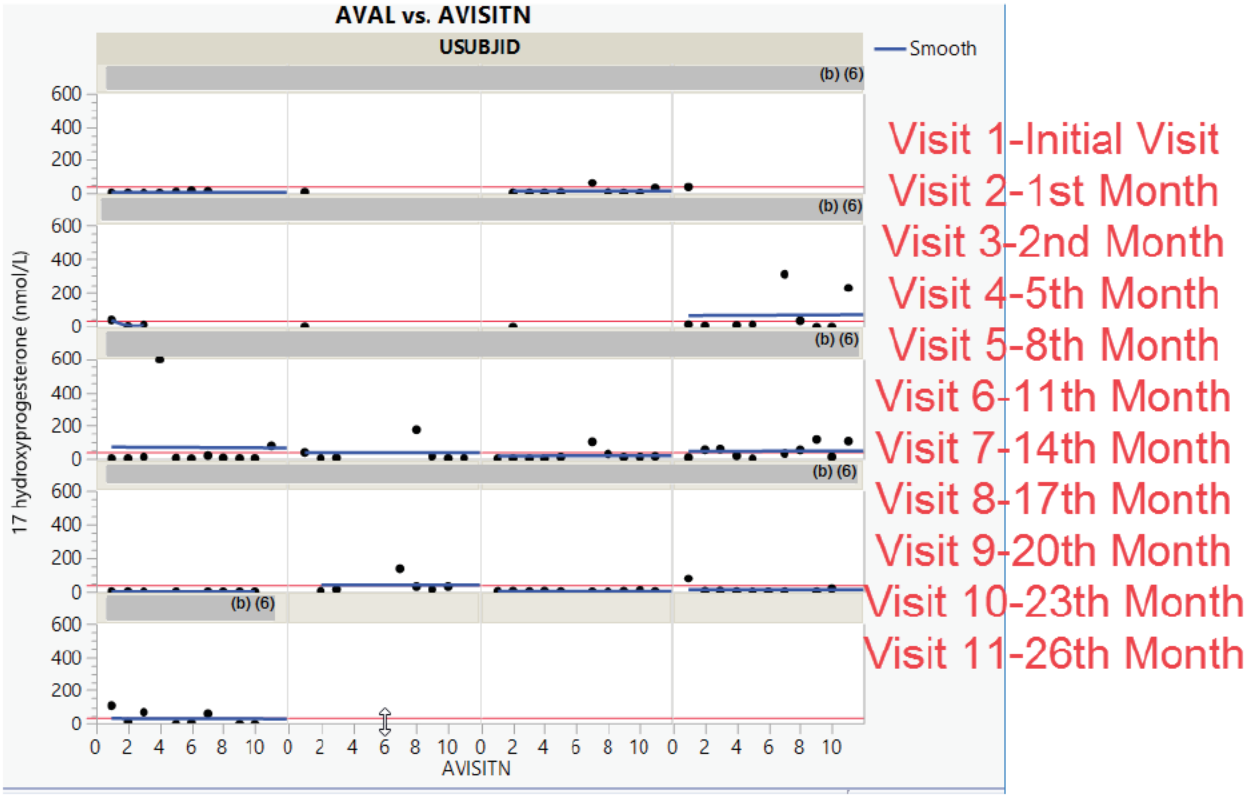
Medical officer's comment-It would have been preferred if the cortisol levels were measured at 60 minutes post dose as was performed in study Infacort 003 as that study showed that most levels return to baseline by 240 minutes post dose. But the limited data here show that even with untimed cortisol measurements the median value was 24.9 nmol/L. The normal range for the assay depending on age and gender varied from 6

to 329 nmol/L. Therefore, 81/122=66% of these measurements were in the normal laboratory range (see cross hatched columns in Fig. 6 above).

Adrenal androgen levels-17-hydroxyprogestroen (17-OHP) from dried blood spot samples in CAH subjects only

While random 17-OHP measurements are generally considered not useful, high values > 40nmol/L indicate under treatment and so should be avoided (Dauber et al. 2010[12]). Consistently excessively high levels of 17-OHP, above the red horizontal line (e.g. 40nmol/L), were not seen during chronic treatment with Hydrocortisone granules but about half of the values that were less than 40nmo/L were still above the normal laboratory reference range as normalization of 17-OHP is not recommended (see Figure 8 below).

Figure 8 Random 17-Hydroxyprogesterone Measurements by Study Visit and Subject in Study Infacort 004



Study 004 ADLB by PARAM=OHP17, AVAL vs VISTN by USUBJID Red line=40 nmol/L

Medical officer's comment-The limited 17-OHP data support control of excessively high

[12] Dauber A, Kellogg M, Majzoub JA **Monitoring of Therapy in Congenital Adrenal Hyperplasia** Clinical Chemistry 56:8 1245-1251 (2010)

hormone levels with chronic treatment.

Tanner Development Stage

All Tanner Development Stage assessments (breast, genitalia, and pubic hair) in the 18 subjects were Grade 1 (pre-pubertal) at baseline, and only 1 subject a 2.5 y/o girl (Subject (b) (6) showed a change during the study with progression of pubic hair to Grade 2 (sparse, pigmented hair mainly on labia), starting with visit 9/month 20 through to the final visit.

Medical officer's comment-A review of Subject (b) (6) growth and laboratory data in Figures 4 through 8 above did not show any evidence of under treatment that might have been responsible for excess androgen production in this patient. Also, a review of this patient's other androgen laboratory values in the ADLB dataset, including serum testosterone, did not identify any values above the upper limit of normal.

Dose/Dose Response

The dose given was the same as the subject's usual immediate release hydrocortisone dose and was adjusted during the study according to the investigator's discretion. No formal dose response testing was performed in this study.

Durability of Response

The fact the height and weight Z-scores were reasonably stable over the course of the study suggest durability of response for the 2 years of the study.

Persistence of Effect

While random cortisol measurements were performed during the study, the timing of the blood draws with respect to the time of the previous hydrocortisone dose was not recorded, so no data is available about the persistence of effect following dosing.

Additional Analyses Conducted on the Individual Trials

None

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section was unnecessary as there was only one trial Infacort 003, with the open label extension, Infacort 004, previously discussed under Sections 6.1 and 6.2. PKPB modeling discussed briefly in Section 4.5 supported the efficacy data.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the post marketing population, it is possible that patients may not follow the warnings and attempt to swallow the capsules whole as opposed to opening them and sprinkling the contents directly onto the tongue or on soft food on a spoon. This may be more common in older children age 6 to 18 years who were not studied in the clinical program. And in fact, in the Safety Update PBRER #4 there was a "medication errors" report of two siblings that routinely swallowed the capsules because they did not like the granules getting stuck in their mouths when taking Hydrocortisone granules at school. While this could represent a choking risk, it is not expected to effect drug absorption significantly as the capsule is made of (b) (4) hypromellose (b) (4). This was confirmed in an *in vitro* study that showed that the delay to dissolution was small and not clinically meaningful.

While the Hydrocortisone granules were designed with an outer coat to mask the bitterness of hydrocortisone, the outer coat may wash off if the granules are left on wet food longer than recommended or if dispersed into liquid prior to ingestion, which is also not recommended. Some children did not like the taste or texture of the formulation so study Infacort 003 was amended to allow for sprinkling on yogurt, or apple sauce to increase palatability. Post marketing efficacy will depend on individual palatability which is likely to affect compliance.

7.2.2. Other Relevant Benefits

Hydrocortisone tablets are licensed in the US under the brand name of Cortef as a variety of generic products ranging in strengths from 5 to 20mg. Doses lower than 5 mg require parents to split or crush the tablets or have a capsule or liquid formulation compounded by individual pharmacists. Problems with the quality of the specifications of these compounded formulations have been reported in the literature resulting in significant under- or over-dosing of subjects. The advantage of Hydrocortisone granules is that they provide capsules with well characterized specifications, with doses as low as 0.5mg, to permit more accurate, individual, dose titration.

7.3. Integrated Assessment of Effectiveness

Treatment of CAH due to 21-hydroxylase deficiency with glucocorticoid replacement therapy began in the 1950s. Hydrocortisone (cortisol) is the preferred glucocorticoid during childhood

because of its short half-life which minimizes the adverse effects typically seen with longer acting and more potent agents such as prednisolone or dexamethasone which can lead to growth suppression. In general, the goal of therapy is to control the symptoms of AI with the lowest dose possible, without compromising growth as is seen with overtreatment. The daily basal cortisol production rate in children has been shown to range between 6.1 ± 1.8 mg/m^2/day in boys to 7.3 ± 1.8 mg/m^2/day in girls. Taking into account the variable bioavailability of oral hydrocortisone formulations due to incomplete intestinal absorption and hepatic metabolism, children with AI alone can be adequately treated with doses 8 to 10mg/m^2/day or less depending on their level of endogenous cortisol secretion. However, the goal of therapy in patients with CAH is not only to replace adrenal glucocorticoids but also to suppress the production of adrenal androgens, thus higher than replacement doses of hydrocortisone are needed in these patients to control other CAH symptoms including virilization, accelerated growth, etc. In randomized trials, doses of hydrocortisone of less than 15mg/m^2/day were shown to provide adequate control of CAH symptoms and to minimize the effect on growth suppression even though they don't normalize plasma 17-OHP concentrations. Dosing three to four times is recommended to better mimic circadian rhythm and to counter long term complications of glucocorticoid replacement. Taking this information into account the Endocrine Society Clinical Practice Guidelines currently recommends dosing with hydrocortisone at 10 to 15mg/m^2/day at least three times a day in growing children with CAH, while dosing can be less frequent, at twice daily, in fully grown patients.

In clinical study Infacort 007, performed in healthy adults, Hydrocortisone granules were shown to be bioequivalent to Cortef tablets which were approved in 1952 and are currently indicated for the treatment of primary or secondary AI, including CAH. Thus, it is expected that efficacy and safety of hydrocortisone for the proposed indication will be the same as for Cortef, the reference listed drug. In clinical study Infacort 003, performed in children with AI, who were less than 6 years of age, single doses of Hydrocortisone granules, were shown to effectively raise median serum cortisol levels to 535 nmol/L (19mcg/dL) with a range of 346 nmol (12.5mcg/dL) to 1445 nmol/L (52mcg/dL) at 60 minutes post dosing. And in the follow up extension study, Infacort 004, Hydrocortisone granules were found to be well tolerated, to control AI symptoms, with no adrenal crisis events and no indication of under-treatment or over-treatment as demonstrated by stable SDS height and weight charts and stable Tanner staging for individual subjects. However, as the applicant has only requested an indication for replacement treatment in subjects with AI and has not requested a separate indication to treat excessive androgen stimulation seen in patients with CAH the later indication should not be approved at this time.

8. Review of Safety

8.1. Safety Review Approach

The safety of hydrocortisone granules is primarily supported by the established safety profile for Cortef tablets. The safety review included additional data on all 24 patients in Infacort 003 and 18 patients in Infacort 004 which enrolled pediatric patients less than 6 years of age with AI. The safety review focused on signs and symptoms of under- or over-dosing with hydrocortisone in patients with AI. Issues related to the potential for a choking hazard were also addressed in relation to concerns identified from postmarketing reports after approval in the EU.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Studies Infacort 001, Infacort 002, Infacort 006 and Infacort 007 were all single dose crossover studies in 100 healthy adult volunteers (80 males and 20 females) and used single doses of Infacort at 0.5 mg, 2 mg, 5 mg, 10 mg and 20 mg. Study 003 was a single dose study in children from infancy to < 6 years in 24 subjects with AI. Study 004 was a follow up long term multiple dose extension of 18 children from Infacort 003 who were treated for a maximum exposure of 872 days or roughly 2 years and 5 months. Of the 18 children 11 were treated for over 23 months.

8.2.2. Relevant characteristics of the safety population:

The safety population for children with AI was essentially the same as the efficacy population for studies Infacort 003 (n=24) and Infacort 004 (n=18). Refer to Sections 6.1.2 and 6.2.2 Tables 10 and 14.

8.2.3. Adequacy of the safety database:

AI is an orphan indication with a very small pediatric population available for study. While 18 subjects is a small study population the fact that most subjects had data out to greater than two years of exposure was helpful in assessing growth and for monitoring for rare but serious events such the risk for adrenal crisis and the need for sick-day rule intervention. All patients were treated three times daily so there is no information to support twice or four times daily dosing from this study population. All but one of the patients had CAH but there is no reason to suspect that patients with other causes for AI, such as the single patient with hypopituitarism (Subject (b) (6)), could not receive adequate cortisol replacement with this new formulation.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The data integrity and submission quality were adequate to perform the safety review. There were no issues with organization of the application or completeness of the safety information that affected the ability to perform an adequate review.

8.3.2. Categorization of Adverse Events

AEs were recorded from the time of the first intake of Hydrocortisone granules until Visit 4 (Day 8 to 11) in study Infacort 003 or until seven days after the last dose administration in Infacort 004. Ongoing AEs were to be followed until subjects returned to baseline or the subject became stable and no further change was expected. Guidelines for assigning severity as mild, moderate or severe were appropriate. Adverse events were considered serious AEs if they resulted in death, were life-threatening, required hospitalization, resulted in a significant disability, or based on appropriate medical judgment might require medical intervention to prevent one of these previously listed outcomes. The number and percentage of subjects with adverse events was tabulated by body system organ class (SOC) and preferred term (PT). A subject with multiple adverse events within a body system or preferred term was only counted once towards the total of that body system or preferred term data. MedDRA Version 18.1 was used for the safety analyses in Infacort 003 and MedDRA Version 21.0 for the safety analyses in Infacort 004. Treatment emergent adverse events (TEAEs) included only events that occurred after intake of Hydrocortisone granules, regardless of severity or relationship to study drug, but events that started before Hydrocortisone granules intake were to be listed if considered applicable. Serious AEs (SAEs) were to be recorded from the time of first intake of Hydrocortisone granules until 7 days following the last administration. Any SAEs experienced after this 7-day period were only to be reported to the applicant if the clinical investigator suspected a causal relationship to Hydrocortisone granules. AEs were considered to be AEs of special interest (AESI)s, whether or not they were considered serious, if they lead to the application of sick-day rules and use of sick-day medication or lead to any medical intervention at a hospital or clinic. In addition, any occurrence of adrenal crisis was to be recorded as an AESI.

8.3.3. Routine Clinical Tests

Baseline blood sampling for cortisol PK, albumin and CBG were the only routine clinical tests performed in Infacort 003. Blood sampling for sodium, potassium, testosterone, renin, hemoglobin, hematocrit was performed as part of routine clinical care normally once a year in Infacort 004 but only testosterone along with other adrenal hormones were reported in the ADLB dataset. No routine clinical tests were reported as AEs according to the applicant.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in Study Infacort 003 or 004.

8.4.2. Serious Adverse Events

There were no serious adverse events in Study Infacort 003.

There were three subjects with a total of 9 SAEs in Study Infacort 004:

1. Subject (b) (6) was a 5-year-old female who had 3 SAEs of gastroenteritis and 2 SAEs of vomiting. These events occurred roughly at 1.5, 4, 8, 12.5 and 13 months after starting dosing with Hydrocortisone granules. There was no explanation for why she had so many events, but her physical exam was notable for an obese abdomen and she was noted to have constipation/obstipation which may have contributed to the GI symptoms. These events lasted between one and four days and responded well to intravenous hydration and stress dosing with hydrocortisone. One episode lasting four days was considered severe on the CRF but miscoded in the AE dataset as moderate and one episode lasting three days was initially listed on the CRF as severe but later changed to moderate. Of the three other episodes two were considered moderate and one was mild in severity. While gastroenteritis with vomiting may be a presentation of AI underdosing, none of these events were believed to be related to the study medication by the clinical investigator, and the girl was continued in the study until the study was terminated.
2. Subject (b) (6) was enrolled into the study as a 36-day old female. She had one SAE of urinary tract infection at one year of age, one SAE of fever with diarrhea at 14 months of age and one episode of pyelonephritis at 25 months of age. All the SAEs were assessed as not related to the study drug.
3. Subject (b) (6) was a 2-year old who had one SAE of erysipelas due to a jellyfish sting requiring hospitalization for 6 days and treated with IV cefuroxime.

In summary, all SAEs in Infacort 004 were considered not related to Hydrocortisone granules treatment by this medical reviewer.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No subjects discontinued studies Infacort 003 or Infacort 004 due to an adverse event. As described previously 6 subjects withdrew from study Infacort 004 due to withdrawal of consent as described under Patient Disposition in Section 6.2.1. Five of these patients withdrew because parents did not like having to wake up their child at night to give the medication. The applicant speculated that children were less cooperative at night and so the added time needed to take the medication may have led to loss of the taste-masking layer on the granules. Also, some of these children had been used to receiving the night time dose as an extemporaneously

prepared sweetened liquid via a syringe which generally did not require them to be woken up to full consciousness, so they preferred the prior formulation.

8.4.4. Significant Adverse Events

According to the sponsor's safety review and AE dataset there were no severe adverse events in Study Infacort 003 or 004. However, as mentioned above one of the cases of gastroenteritis in Subject (b) (6) was labeled as severe in the subject's CRF, and one case was changed from severe to moderate, but these events were not considered related to treatment with Hydrocortisone granules.

There were 6 AEs of special interest (AESI)s in 3 subjects in Infacort 004:

1) Subject (b) (6) reported 2 AESIs - pharyngotonsillitis at 6 months after the first dose of Hydrocortisone granules and scarlet fever at 14.5 months after the first dose.
2) Subject (b) (6) reported 3 AESIs - obstructive bronchitis at 19 months after the first dose of Hydrocortisone granules, URI with conjunctivitis at 21 months after the first dose and influenza with fever, vomiting and cough at 23 months after the first dose.
3) Subject (b) (6) reported 1 AESI - tonsillitis with vomiting at 21.5 months after the first dose of Hydrocortisone granules.

In all cases the dose of Hydrocortisone granules was increased to give stress doses. All events were considered non-serious and not related to Hydrocortisone granules treatment and subjects fully recovered.

There were 172 episodes invoking sick-day rules in 13 subjects. The most common reason was fever resulting in 101 episodes in 13 subjects, followed by 47 episodes of "other" in 10 subjects, 14 episodes of vomiting in 5 subjects, and 9 episodes of diarrhea in 2 subjects. The episodes of "other" were reviewed by this medical reviewer from Listing 16.2.6.1. and the most common reason for "other" were some type of infection (i.e. gastroenteritis, URI, otitis media, enterovirus, erysipelas, coxitis fugax, infection, scarlet fever); injuries (i.e. fall, cut, scald, jellyfish sting); dental or surgical procedures, and emotional or physical stress (i.e. excitement from first day in kindergarten, birthday party, sleepover, stomachache, headache, prolonged hiking).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In the single dose studies in healthy volunteers the only TEAEs seen in more than one subject were headache (n=3), and oral hypoesthesia (n=2). The oral hypoesthesia was considered drug related and lasted only 5 minutes before it resolved on its own.

The most common TEAEs in Study Infacort 003 were diarrhea (n=3, 12.5%), vomiting, and rash (n=2, 8% each) and fatigue, infantile spitting up/posseting, and hyperhidrosis (n=1, 4% each). The applicant's review of the two cases of vomiting suggested they were not likely to be drug

related as one occurred one and a half hours after dosing and appeared to be related to medical procedures that were done at the time and the other episode occurred six and a half hours after dosing. The two cases of rash involved a suspected mosquito bite and exanthema on the left back of neck, both not typical symptoms of drug related rash.

The most common TEAEs in Study Infacort 004 were pyrexia (45 events in 10 subjects), followed by gastroenteritis (15 events in 9 subjects), viral upper respiratory tract infection (22 events in 8 subjects) and vomiting (14 events in 7 subjects). Most TEAEs were infections which are common in young children over the course of two years and were unlikely to be drug related.

Table 18 TEAEs in Infacort 004 in Two or More Subjects

Preferred Term	Pt number	%
Pyrexia	10	56
Gastroenteritis	9	50
Viral upper respiratory tract infection	8	44
Vomiting	7	39
Viral infection	6	33
Conjunctivitis	5	28
Otitis media viral	3	17
Tonsillitis	3	17
Body temperature increased	2	11
Bronchitis	2	11
Dental caries	2	11
Diarrhoea	2	11
Genitourinary operation	2	11
Pharyngitis	2	11
Respiratory tract infection	2	11
Rhinitis	2	11

Source 004 ADAE by (SUBJID,AEDECOD) by AEDECOD

Of note no AEs of choking or drug medication errors or product use errors were seen in studies Infacort 003 and 004.

8.4.6. Laboratory Findings

The laboratory datasets for studies Infacort 003 and 004 consisted of blood spot sample analysis of 16 endogenous hormones which was an exploratory analysis as the methodology

has yet to be validated. The Infacort 003 dataset also included baseline only data for albumin and cortisol binding globulin which does not provide any additional useful safety information. According to the applicant no laboratory values were considered to be clinically significant or to represent an AE.

8.4.7. Vital Signs

There was a fair amount of variability in HR and BP which was attributed to the usual pattern in excitable children and was not considered clinically significant by the clinical investigators involved. AEs related to changes in vital signs included two subjects with AEs of body temperature increased, ten subjects with AEs of pyrexia and one subject with secondary hypertension. However, none of these changes in vital signs were considered related to the study treatment, with most of the changes in body temperature were associated with ongoing infections. More important, none of the subjects had hypotension AEs as a possible sign of AI.

8.4.8. Electrocardiograms (ECGs)

Not applicable. ECGs were not conducted in studies Infacort 003 and 004.

8.4.9. QT

Not applicable.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Choking Hazard

Despite appropriate labeling stating that these capsules should not be swallowed whole, but instead opened and the contents dispensed, there is always the possibility that a subject may inadvertently attempt to swallow the intact capsule. And in fact, in the 4-month Safety Update PBRER #4 Section 3.3, there was a report of two siblings that routinely swallowed the capsules because they did not like the granules stuck in their mouths when taking Hydrocortisone granules in school, so this is a real concern and not just theoretical. As discussed previously under Section 7.2.1 , the capsule is composed of HPMC Hypromellose which will rapidly dissolve in the stomach and so should not significantly affect drug absorption. However, since these capsules are fairly large there is the concern that they could present a choking hazard in children who may attempt to swallow them. Part of the reason they were developed as large as they are is to discourage attempts at swallowing. Assuming parents receive correct initial instructions on proper drug administration this issue it is unlikely to be problem. The concern is

likely to be greatest in patients whose parents are not adequately educated with the initial prescription, which likely would represent parents with poor English language skills and those in vulnerable family situations. There is also the concern that if patients are in an unusual setting like a new daycare, or a sleepover at a friend or relatives house, especially for the first time, that parents or caretakers make the effort to adequately convey proper drug administration with the capsules.

Apart from the risk of choking on the capsules, there were several reports of gaging in newborn infants, which were not described as choking, as the child was not coughing, but more related to attempts to expel the granules or "retching" or spitting out of the granules which could put the children at risk of aspiration of the granules or underdosing if the granules are spit out (See PBRER #2 & #4 Section 3.3). While the granules are designed with an outer layer to mask their bitter taste, with time that layer can be dissolved, and the granules become less palatable. This apparently was also an issue when trying to dose children at night when they had to be woken from their sleep, as these children took longer to take their medicine. If children are to be woken up from sleep at night, every effort should be made to make sure they are conscious enough to swallow before the granules are administered as this could also lead to aspiration of the granules when liquid is used to wash in the granules. Without adequate liquid to wash in the granules they are likely to linger in the child's mouth and eventually be spit out. With respect to these concerns it is important that premature infants and newborns who do not have an adequate suck or gag reflex not be administered this formulation as they would be at greater risk for aspiration.

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

Both underdosing and overdosing can result in suppression of linear growth in children with AI. In general, the goal of therapy is to control the symptoms of AI with the lowest dose possible, without compromising growth that is seen with overtreatment. Standard deviation scores for height and weight for children in study Infacort 004 were previously described in detail as part of the secondary endpoints in Section 6.2.2. In summary, there was no indication for under-treatment or over-treatment with chronic treatment with Hydrocortisone granules as demonstrated by stable SDS height and weight charts.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was one report of a subject being given a higher dose than planned in Study Infacort 004. Subject (b) (6) was given a higher dose at the 15:00 timepoint (2 mg) instead of the planned 1 mg capsule but there were no consequences and the subject reported no AEs as a result. The median terminal half-life of Hydrocortisone granules is about one and a half hours but can range from 1 to 4 hours (See Infacort 007). So, while there is no antidote for overdose, and acute toxicity is rare, patients can be monitored as needed until the drug is eliminated.

Drug abuse is unlikely with Hydrocortisone granules, but it is possible that there could be off-label use in adults who have problems with swallowing tablets. Although the low dose of these capsules would require multiple doses to provide the standard adult dose which could discourage over usage.

While high dose corticosteroids can result in suppression of the hypothalamic-pituitary-adrenal axis resulting in inadequate cortisol production, that would not be an issue with the replacement doses used here for AI. Some subjects have reported psychological disturbances associated with withdrawal from corticosteroids, but that is less likely in patients with AI who are on chronic glucocorticoid replacement.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Issues from postmarketing reports dealing with the risk of choking from inappropriately swallowing the capsules, retching/ spitting out the granules due to palatability issues or poor suck or gag reflex increasing the risk of aspiration were previously discussed under 8.5.1 Choking Hazard. Additional safety concerns identified in the foreign postmarketing reports also previously described in more detail under Section 3.3 Foreign Regulatory Actions and Marketing History include:

- inability to get granules to come out of the capsule after wetting the rim when trying to place the contents on the tongue, and
- pooling of contents from several capsules into one capsule to provide a single capsule for dispending of the dose at school, which can result in underdosage if there is spillage

or could result in wrong doses being administered if the capsules with pooled contents are later mixed up with the original capsules.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety concerns in the postmarketing setting are likely to be more of an issue than was seen in the clinical trials where investigators were more likely to ensure parents or caretakers are given proper initial instructions on proper drug administration. The limited postmarketing data from the EU discussed previously in Sections 8.5.1 and 8.9.1 suggest some children may inappropriately try to swallow capsules, which poses a choking risk, and that palatability/spitting up may still be an issue in some younger children especially during night time dosing. It is important that healthcare providers emphasize the need to follow proper dose administration instructions and remind parents/caretakers about the need to convey such information to whomever might be responsible for dosing their child in school, daycare, or at a friend's/relative's house during an overnight stay.

There are no additional safety concerns anticipated from off-label use in adults who use the capsules due to problems with swallowing hydrocortisone tablets.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Drug class symptoms from over treatment with glucocorticoids include weight gain, decreased height velocity, hyperglycemia, hypertension, edema, easy bruising, muscle weakness, red round face, depression or mood swings, which were not seen in the pediatric clinical trials. The treatment related adverse events seen in the clinical trials were mostly infections (e.g. pyrexia, gastroenteritis, URI, viral infection etc.) which are common in young children over the course of two years and were unlikely to be drug related. However, several potential safety concerns were observed in the post marketing reports from the EU which likely need to be addressed as part of the risk benefit assessment. While there were no episodes of clear choking from someone inappropriately trying to swallow the capsules, there were two siblings who routinely swallowed the capsules to avoid having the granules in their mouths while they were in school. The concern is that these capsules are large and that this could be a choking hazard. In fact, the capsules were made larger partially to discourage attempts at swallowing. There were also several reports of younger children spitting up the granules/which was described as retching as opposed to choking which could result in under dosing. While in general palatability was good for most patients, not all patients liked the taste or granule texture. Five mothers withdrew their children from the open label extension study do to having to give the night time dose which involved waking up the children. The applicant believed that sleepy children might have

taken longer to swallow the granules so the taste masking outer cover might have been removed and made them less palatable. The granules need to be washed in with a follow up drink which also requires the child to be more conscious when woken up to avoid aspiration of the granules. If that is not done it is possible that some granules may remain in the mouth and be spit out when the child goes back to sleep resulting in under dosing. Some of these children had been used to receiving the night time dose as an extemporaneously prepared sweetened liquid via a syringe which generally did not require them to be woken up to full consciousness, so they preferred the prior formulation. However, such compounded formulations are not recommended as they have been shown to lack consistency and resulting in inaccurate dosing. Finally, there was one case where a mother mixed the contents of two capsules into a single capsule to be given at school for convenience. That could result in spillage and underdosing or if the new capsule is somehow mixed up with the original capsules it could lead to over dosing. It might be helpful if the treating physician dispensed the first dose in their office to go over any questions about administration. In general, with adequate labeling most primary caretakers should be able to understand the administration instructions; the concern is greatest for caretakers with language difficulty or if the child is in vulnerable home situation. Also, of concern would be when the child is in a new situation, such a first sleepover, or spending the day with relatives for the first time or in a new daycare, with poorly trained personnel. In conclusion it is this medical reviewer's assessment that these safety concerns can be dealt with appropriate labeling and adequate instructions prior to first use.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The approved indication should be "replacement therapy of adrenal insufficiency". "Treatment of CAH", which requires higher doses of hydrocortisone to suppress adrenal androgens should not be approved at this time and dosing information for the treatment of CAH should not be included in the label.

Under the Warnings and Precautions Section 5 (b) (4) needs to be split up into individual sections: Effect on Growth, Cushing syndrome due to use of excessive doses of corticosteroids, Decrease in Bone Mineral Density, and Psychiatric Adverse Reactions. Excretion of granules (b) (4) should

(b) (4) placed under Patient Counseling Information Section 17.

(b) (4)

(b) (4)

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

The main safety concern is the risk of choking from swallowing the capsule en bloc, additional safety concerns revolve around

- poor palatability in some younger children resulting in retching or spitting up of the capsules resulting in underdosing,
- use in children with poor suck or gag reflex increasing the risk of aspiration, and
- misadministration by combining capsule contents into a single capsule for easier dosing, which could result in spillage of contents, or mixing up of the pooled capsules with the original capsules and improper later dosing.

It is this medical reviewer's assessment that these concerns can be adequately addressed with proper labeling, and enhanced pharmacovigilance. Should the enhance pharmacovigilance provide signals for maladministration as described above, a follow up dear healthcare provider letter focused on the identified concerns could help to minimize the observed safety concerns.

12. Postmarketing Requirements and Commitments

No postmarketing studies are necessary to address the potential safety concerns. However, it is recommended that enhanced pharmacovigilance looking for signals of maladministration be included as part of the approval.

13. Appendices

13.1. References

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13.2. Financial Disclosure

There were no financial disclosures for the bioequivalence study, Infacort 007, in healthy adults. For the pediatric clinical studies, Infacort 003 and 004, (b) (6)

(b) (6)

Covered Clinical Study (Name and/or Number): Infacort 007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Infacort 003 and 004

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 5		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM A LUBAS
09/01/2020 09:09:51 PM

MARINA ZEMSKOVA
09/02/2020 09:07:41 AM
I concur with Dr. Lubas