Amsterdam, 19 June 2025
EMA/CHMP/570616/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Hydrocortisone Aguettant

International non-proprietary name: hydrocortisone

Procedure No. EMEA/H/C/005201/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AChR	Acetylcholine Receptor
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AP	Applicant's Part (or Open Part) of an ASMF
AP-1	Activator Protein 1
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AUC	Area Under the Curve
BPD	Bronchopulmonary Dysplasia
BW	Body Weight
CBG	Corticoid Binding Globulin
CEP	Certificate of Suitability of the Ph. Eur.
CFU	Colony Forming Units
CHMP	The Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
CLD	Chronic lung disease
CMS	Concerned Member State
CoA	Certificate of Analysis
COX	Cyclooxygenase
CPAP	Continuous positive airway pressure
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRF	Corticotropin Releasing Factor
CRH	Corticotrophin Releasing Hormone
CRS	Chemical Reference Substance (official standard)
CS	Corticosteroids
CsA	Cortisol and cyclosporine
CSR	Clinical study report
CV	Coefficient of Variation
CVMP	Committee for Veterinary Medicinal Products
CYP	Cytochrome P
DA	Days of amenorrhea
DNA	Deoxyribonucleic Acid
DP	Drug Product
DPM	Drug Product Manufacturer
DQ	Developmental quotient
DS	Drug Substance
DSC	Differential Scanning Calorimetry
DSM	Drug Substance Manufacturer

DX	Dexamethasone
EDQM	European Directorate for the Quality of Medicines
EGL	External Granular Layer
ELBW	Extremely low birth weight
EPAR	European Public Assessment Report
FAS	Full analysis set
FiO2	Fraction of inspired oxygen
FP	Finished Product
FPM	Finished Product Manufacturer
GA	Gestational age
GC	Glucocorticoid
GD	Gestation Days
GI	Gastro-Intestinal
GLMM	Generalized Linear Mixed Model
GLP	Good Laboratory Practices
GR	Glucocorticoid Receptor
GREs	Glucocorticoid Response Elements
HC	Hydrocortisone
HCHS	Hydrocortisone hemisuccinate
His	Histidine
(HP)LC	(High-Performance) Liquid Chromatography
(HS-)GC	(Headspace-) Gas Chromatography
HPA	Hypothalamic-Pituitary-Adrenal
Hsp90	Heat-Shock Protein 90
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP	Inductively Coupled Plasma
IGF	Insulin-like growth factor
IGFBP	Insulin-like Growth Factor-Binding Protein
IL-6	Interleukin-6
IM	Intramuscular
IP	Intraperitoneally
IPC	In-Process Control
IPTW	Inverse probability of treatment weighting
IQ	Intelligence quotient
IR	Infrared (spectroscopy)
ITT	Intention to treat
IU	International Units
IUGR	Intra uterine growth retardation
IV	Intravenous
IκBα	Inhibitor of κB α
(LD/HD)PE	(Low Density / High Density) Polyethylene
LOA	Letter of Access
LOD	Limit of Detection

LOQ	Limit of Quantitation
LT	Less Than
MAA	Marketing Authorization Application
MAH	Marketing Authorisation Holder
MDD	Maximum Daily Dose
mFAS	Modified Full analysis set
MGR	membrane GR
MoA	Mechanism of Action
MRI	Magnetic resonance imaging
MRL	Maximum Residue Limit
MS	Mass Spectrometry
NA	Not available
NDI	Neurodevelopmental impairment
NF-κB	Nuclear Factor kappa-light-chain-enhancer of Activated B Cells
nGREs	Negative Glucocorticoid Response Elements
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
NNH	Number needed to harm
NNT	Number needed to treat
NOEL	No Observed Effect Level
NS	Not significant
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OECD	Organization for Economic Co-operation and Development Business
OES	Optical Emission Spectrometry
OOS	Out of Specification
OR	Odds ratio
PCN	Pregnenolone 16αCarbonitrile
PDA	Parental Drug Association
PDE	Permitted Daily Exposure
PES	Polyethersulfone
Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PLA-2	Phospholipase A2
PMA	Postmenstrual age
PND	Postnatal Day
PNS	Post natal steroids
PP	Polypropylene
PVC	Polyvinylchloride
PVDF	Polyvinylidene fluoride
PVL	Periventricular leukomalacia
QP	Qualified Person

RBL	Revised Brunet-Lezine
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RR	Risk ratio
RSD	Relative Standard Deviation
(R)RT	(Relative) Retention time
S(m)PC	Summary of Product Characteristics
SAE	Serious adverse event
SCE	Sister-Chromatid Exchanges
SD	Standard Deviation
SLPI	Secretory Leucocyte Protease Inhibitor
SM	Starting Material (of drug substance synthesis)
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TF	Transcription Factor
TGA	Thermo-Gravimetric Analysis
TK	Thymidine Kinase
TLC	Thin-Layer Chromatography
TOP	Retinopathy of prematurity
TTC	Threshold of Toxicological Concern (acc. to ICH M7)
USP	U.S. Pharmacopeia
UV	Ultraviolet (spectroscopy)
w.r.t.	With respect to
WA	Weeks of amenorrhea
WM	White matter
XR(P)D	X-Ray (Powder) Diffraction

1. CHMP recommendation

Based on the review of the data on quality, safety and efficacy, the hybrid application for Hydrocortisone Aquettant in the prevention of BPD in preterm infants born between 24 and 28 weeks of postmenstrual age, is not approvable since 'major objections' pertaining to quality and B/R have been identified, which preclude a recommendation for marketing authorisation at the present time.

In addition, satisfactory answers must be given to the 'other concerns' as detailed in the LoOI.

1.1. Questions to be posed to additional experts

Not applicable.

1.2. Proposal for inspection

1.2.1. GMP inspection(s)

Not applicable.

1.2.2. GCP inspection(s)

Not applicable.

1.3. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4. Derogation(s) from market exclusivity

Not applicable.

2. Executive summary

2.1. Problem statement

Bronchopulmonary dysplasia (BDP) is a chronic lung disease which affects premature infants. Premature infants requiring treatment with supplemental oxygen or long – term oxygen are at a higher risk. The alveoli of these infants tend to be not mature enough to function normally. BDP is more common in infants with low birth weight and those who receive prolonged mechanical ventilation support to treat the respiratory distress syndrome.

BPD is now recognised as the result of a disruption in lung development in response to both antenatal injury and repetitive postnatal injury. Consequently, lung development is markedly impaired, which leads to persistent airway and pulmonary vascular disease that can affect adult lung function. Postnatal adaptation of the preterm lungs to breathing at birth is challenged by initial lung injury owing to surfactant deficiency, exposure to increased oxygen, mechanical ventilation, inadequate nutrition, infection and inflammation, which together provide considerable hurdles to normal pulmonary growth and repair and result in a loss of alveolar surface area that has lifelong consequences.

It results in significant morbidity and mortality. The definition of bronchopulmonary dysplasia has continued to evolve primarily due to changes in the population, such as more survivors at earlier gestational ages, and improved neonatal management including surfactant, antenatal glucocorticoid therapy, and less aggressive mechanical ventilation.

The cause of BDP is linked to prolonged high oxygen delivery in premature infants causing necrotizing bronchiolitis, alveolar septal injury with subsequent inflammation and scarring. Today with the introduction of surfactant therapy and high frequency ventilation and optimised oxygen supplementation infant with BDP experience a much milder injury without necrotising bronchiolitis and alveolar septal necrosis. In these much milder cases usually uniformly dilated acini with thin alveolar septa and little or no interstitial fibrosis are present.

The classic earlier criteria for diagnosis were:

1. Positive pressure ventilation during the first two weeks of life for a minimum of three days.
2. Clinical signs of abnormal respiratory function.
3. Requirements for supplemental oxygen for longer than 28 days of age to maintain PaO2 above 50 mm Hg.
4. Chest radiograph with diffuse abnormal findings characteristic of bronchopulmonary dysplasia

In 2006 the National Institute of Health published the updated criteria for BDP (for neonates treated with more than 21% oxygen for at least 28 days):

Mild

- Breathing room air at 36 weeks' post-menstrual age or discharge (whichever comes first) for babies born before 32 weeks, or
- breathing room air by 56 days' postnatal age, or discharge (whichever comes first) for babies born after 32 weeks' gestation.

Moderate

- Need for <30% oxygen at 36 weeks' postmenstrual age, or discharge (whichever comes first) for babies born before 32 weeks, or
- need for <30% oxygen to 56 days' postnatal age, or discharge (whichever comes first) for babies born after 32 weeks' gestation.

Severe

- Need for >30% oxygen, with or without positive pressure ventilation or continuous positive pressure at 36 weeks' postmenstrual age, or discharge (whichever comes first) for babies born before 32 weeks, or
- need for >30% oxygen with or without positive pressure ventilation or continuous positive pressure at 56 days' postnatal age, or discharge (whichever comes first) for babies born after 32 weeks' gestation (Kinsella et al 2006).

The definition of BDP used in the PREMILOC this study was the need for ventilatory support and / or administration of supplemental oxygen. It was defined as ventilatory support using either mechanical or continuous positive airway pressure (CPAP) ventilation, or spontaneous ventilation with the need for FiO2 ≥ 30%, or spontaneous ventilation with FiO2 < 30% but a failure in oxygen reduction test (Walsh test) showing true oxygen dependency. Only neonates with gestational age between 24+0 and 27+6 weeks of gestation were included in the study.

BDP is among the most common and serious sequelae of preterm birth. BPD affects at least one-quarter of infants born with birth weights less than 1500g. The incidence of BPD increases with decreasing gestational age and birth weight (Jensen & Schmidt 2014).

In 10 European regions, rates of BPD ranged between 10.5% and 21.5% for infants born less than 32 weeks of gestation in 2003. A wide variability of BPD between European regions may be explained by different local practices; the strongest association however was with degree of immaturity (Zeitlin 2008).

While some reports indicate BPD rates are beginning to decline, the majority of studies suggest that rates remained stable or even increased during the past two to three decades, possibly due to increased survival of the highest risk infants (Jensen & Schmidt 2014).

There is currently no approved treatment with the indication "Prevention of BPD in preterm infants born less than 28 weeks of gestation" or with the indication "treatment".

The currently applicable therapeutical modalities are presented below according to Hennely (2021).

Table 1: Therapeutical modalities

Intervention	**Use**	**Proposed mechanism of action**	**Evidence**
Non-invasive ventilation	Prevention	Decreases lung injury due to barotrauma and volutrauma by avoidance of intubation	Meta-analyses showing reduction in BDP or death support use of early CPAP
Oxygen saturation targets	Prevention	Avoids lung injury secondary to hyperoxia-induced free radicals	Increase in mortality, but no difference in rates of BDP with lower (85-89%) oxygen saturation targets. Recommend targeting SpO_2 levels in low 90s
Surfactant	Prevention	Prevents and treats respiratory distress syndrome and facilitates early extubation	Early surfactant administration shown to decease risk of BDP Less invasive techniques for surfactant administration are promising and may reduce BDP
Caffeine	Prevention	Reduces duration of mechanical ventilation by improving respiratory drive, tidal volume, lung compliance and reducing total lung resistance. Has anti-inflammatory and diuretic effects	Use of early caffeine is associated with 36% decrease in BDP. Early caffeine use (first 10 days of age) recommended
Vitamin A	Prevention	Promotes respiratory cell growth and differentiation	Decrease in incidence of BDP with intramuscular administration of vitamn A. Use recommended depending on local incidence of BDP

Diuretics	Prevention	Reduces interstitial pulmonary oedema and fluid overload	Short term improvement in pulmonary mechanics. Some evidence to suggest use of furosemide decreases BDP, other found no difference. Insufficient evidence to make recommendation.
	Management		Short term decrease in airway decrease in airway resistance and increase in airway compliance with furosemide in infants with BDP. May improve respiratory scores, lung mechanics and decrease fraction of inspired oxygen. No difference in mortality with loop diuretic use in infants with severe BDP
Antenatal steroids	Prevention	Stimulates surfactant production	Decreased frequency and severity of RDS and need for mechanical ventilation. No difference in overall risk for BDP
Postnatal steroids	Prevention	Anti-inflammatory properties ameliorate inflammation secondary to ventilator induced injury, oxygen toxicity or infection	Early (<7 days of age) use of dexamethasone associated with significant adverse effects and is not recommended. `strong evidence to support later use of dexamethasone in infants at hight risk of developing severe BDP. Emerging evidence to suggest that use of HC may improve BDP-free survival and avoid neurotoxicity. Early use of inhaled corticosteroids decreases BDP but increases mortality and is recommended. Promising data showing decreased risk of BDP when intratracheal corticosteroids are administered with surfactant.

	Management		Inhaled corticosteroids may improve oxygenation, increase airway compliance, functional residual capacity, decrease airway resistance. Oral prednisolone may facilitate oxygen wean in established BDP.
PDA closure	Prevention	Reduces pulmonary interstitial oedema caused by increased pulmonary flow through a hemodynamically significant PDA	Inconclusive evidence to suggest PDA closure leads to reduction in risk of BDP. Possible benefit in a subset
Bronchodilators	Management	Improves short term lung mechanics by increasing compliance and decreasing pulmonary resistance by dilating smaller airways with muscular atrophy	Lack of evidence supporting use of management of BDP. May have short term benefits when strong component of bronchospasm is present
Macrolides	Prevention	Treats Ureaplasma infections and has anti-inflammatory properties	Few showing small risk reduction in BDP when used prophylactically, larger studies needed to establish safety and effectiveness
Abbreviations: PMA – postmenstrual age; NIH – National Institute of Health; NICHD – National Institute of Child Health and Human Development; CPAP – continuous positive airway pressure; RDS – respiratory distress syndrome; PDA – patent ductus arteriosus			

To date, only steroids and nitric oxide have been evaluated in large- scale trials for prevention of BPD. Caffeine and surfactant provide symptomatic management but do not directly target the disease pathophysiology itself.

2.2. About the product

Hydrocortisone is a very well-known glucocorticoid used since decades worldwide. The drug has well-established clinical use in indications involving both systemic and local administration. It is indicated in adults and children (including neonates) in a large number of therapeutic domains making use of its anti-inflammatory and immunosuppressant properties.

Hydrocortisone belongs to the pharmacotherapeutic group: Corticosteroids for systemic use; Glucocorticoids, ATC code: H02AB09.

The active compound of Hydrocortisone Aguettant is hydrocortisone (HCHS), which is, at a concentration of 1.33 mg/ml (corresponding to 1.0 mg/ml of hydrocortisone anhydrous base).

Hydrocortisone Aguettant is a clear colourless solution resulting from the reconstitution of two vials each containing a sterile lyophilisate or a sterile reconstitution solvent, by means of two separate sterile vial adapters (reconstitution system). It is immediately slowly administered intravenously after reconstitution in a final concentration of 1 mg/ml.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The PREMILOC study was performed to assess the efficacy and safety of HC for prevention of BPD in very preterm infants. It was a prospective, placebo-controlled, randomised, multicentre study initiated by hospital experts in an academic environment and conducted in France.

The applicant highlighted that as this is an academic study, some analyses that are usually part of the initial statistical analysis plan, especially regarding safety, were performed as post hoc analyses only. While this is not recommended in the Good Clinical Practice (GCP), the applicant considered it is common practice with academic studies and obtained results remain useful. However, there are severe issues that remain on the PREMILOC study.

No scientific advice was sought for this application.

2.4. General comments on compliance with GMP, GLP, GCP

GMP-Drug Substance

A qualified person (QP) declaration is presented by the drug product manufacturer, confirming that the drug substance is manufactured according to current EU GMP for active substances. The basis of the QP declaration is on-site audits on the manufacturing sites involved in the synthesis of hydrocrotisone hydrogen succinate.

GMP-Drug Product (Powder and diluent)

A GMP certificate issued by the French Health Authorities confirms that the drug product manufacturer is authorised for manufacture of aseptically prepared products. It is also authorised for testing the sterility. The vials and the stoppers are sterilised by the drug product manufacturer.

GCP

The study was conducted prior the purchase of the database by the applicant. The study was undertaken by a French hospital. The initial analyses were published in the Lancet in 2016 and also in 2024 (Baud et al 2024).

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

Article 10(3) of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.

The reference product (from Upjohn) was used in the pivotal clinical trial. *In vitro* comparability to Hydrocortisone Aguettant is shown as detailed in the quality part.

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Hydrocortisone Upjohn 100 mg, solution for infusion
- Marketing authorisation holder: SERB
- Date of authorisation: 25-07-1977
- Marketing authorisation granted by:

- Member State (EEA): France

  - National procedure

- Marketing authorisation number: CIS 6 158 141 7

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Hydrocortisone Upjohn 100 mg, solution for infusion
- Marketing authorisation holder: SERB
- Date of authorisation: 25-07-1977
- Marketing authorisation granted by:
  - <Member State (EEA): France

    - National procedure

- Marketing authorisation number: CIS 6 158 141 7

2.5.2. Orphan designation

Not applicable.

2.5.3. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.4. Derogation(s) from orphan market exclusivity

Not applicable.

2.5.5. Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0358/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002305-PIP01-17-M01 was completed.

The PDCO issued an opinion on compliance for the PIP with an agreement of a paediatric investigation plan and on the granting of a waiver for hydrocortisone.

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, the applicant submitted for agreement to the European Medicines Agency on 23 October 2018 an application for a PIP for the above-mentioned medicinal product and a waiver under Article 13 of said Regulation.

The Paediatric Committee, having assessed the proposed PIP in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

- to agree the PIP in accordance with Article 17(1) of said Regulation.
- to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(a) of said Regulation, on

the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population and Article 11(1)(b) of said Regulation, on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified subset(s) of the paediatric population.

The PIP was agreed for the condition of Prevention of bronchopulmonary dysplasia (BPD) with the following indication:

Prophylactic use in preterm infants born at or less than 28 weeks of gestation to prevent bronchopulmonary dysplasia (BPD).

The waiver applies to:

- preterm newborn infants from 28+0 to less than 37+0 weeks gestational age (GA)
- powder and solvent for solution for injection; intravenous use
- on the grounds that the specific medicinal product is likely to be ineffective
- and
- term newborn infants (from birth to less than 28 days), infants and toddlers (from 28 days to less
- than 24 months), children (from 2 to less than 12 years of age) and adolescents (from 12 to less than 18 years of age)
- powder and solvent for solution for injection, intravenous use

on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as powder and solvent for solution for injection (powder for injection) containing an equivalent of 1 mg of hydrocortisone base after reconstitution and co-packaged vial adapters.

Due to losses due to reconstitution, for both vials overfilling are established.

The active substance introduced in the manufacturing process is hydrocortisone hydrogen succinate, experiencing in-situ formation to hydrocortisone sodium succinate.

Other ingredients are:

Powder: trehalose dihydrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium hydroxide and concentrated or diluted phosphoric acid.

Solution: glucose monohydrate, water for injection

The product is available in glass vials (2ml), closed with an halobutyl rubber stopper for the powder and the solvent.

The two attached vial adapters are used for reconstitution.

3.1.2. Active substance

3.1.2.1. General information

The active substance introduced in the manufacturing process is hydrocortisone hydrogen succinate (Ph. Eur. monograph 0768). The drug substance holds a certificate of suitability.

The drug substance is white and crystalline. It is not soluble in water but prepared with the aid of sodium hydroxide a water-soluble salt is formed.

3.1.2.2. Manufacture, process controls and characterisation

Due to the fact that a CEP is provided for the drug substance, no information on synthesis/or manufacture is included here.

3.1.2.3. Specification(s)

Specification (as provided by the applicant)

The specification complies with the Ph. Eur. monograph 0768. Other specification parameters (and limits) for impurities and residual solvents comply with additional information as stated on the CEP.

The specification mentions additional parameters (relevant for this dosage form) like bacterial endotoxins, microbial contamination (TYMC/TAMC) and specific micro-organism. These additional tests and their limits are acceptable and now headlined correctly. In the last steps of the synthesis of the active substance, Ph. Eur purified water is used in line with the Guideline on the quality of water for pharmaceutical use EMA/CHMP/CVMP/QWP/496873/2018.

Analytical procedures and reference standards

Test methods used in the specification of the drug substance are those described in Ph. Eur. monograph 0768 or attached on the CEP (residual solvent by GC).

Additional analytical methods, as used for bacterial endotoxins, determination of microbial contamination and for specified microorganism are those of Ph. Eur. current edition.

Validation of analytical methods stated on the CEP is not necessary. The analytical methods for bacterial endotoxins, microbial contamination and specified micro-organism are validated for their use with the drug substance. Hydrocortisone hydrogen succinate does not negatively influence these tests.

Batch analysis

Batch analysis data of three batches drug substance are provided. All three batches were manufactured in 2021, which is considered acceptable. Each batch is tested by the drug substance manufacturer as well as the drug product manufacturer and data are quite similar.

3.1.2.4. Stability

The re-test period, as mentioned on the CEP, is 3 years if stored in double polyethylene bags, placed in a polypropylene container.

3.1.3. Finished medicinal product

The finished product consists of 1) a freeze- powder and 2) a glucose. The following overview is therefore subdivided in evaluation of the powder and the solution. In some cases, there is some overlapping information between the two chapters.

Powder

3.1.3.1. Description of the product and pharmaceutical development

Description of the product

From a pharmaceutical quality point of view, the description of powder and solution (the two drug products) is now updated as requested. One row includes the amount of all substances, including overfilling, per vial, whereas, an additional row includes the amount of the substances as administered ('Quantity for 1 mg of hydrocortisone, as labelled'), to focus on what is given to the patient is acknowledged.

In addition, the drug substance is stated as in-situ formed 'Hydrocortisone Sodium Succinate', the weighed amount 'prepared from Hydrocortisone hydrogen succinate monohydrate' and is expressed as 'anhydrous Hydrocortisone hydrogen succinate' and the 'Equivalent to anhydrous Hydrocortisone basis'.

Freeze-dried vial (lyophilizate):

The formulation contains 1.34 mg of Hydrocortisone sodium succinate equivalent to 1.28mg of anhydrous Hydrocortisone hydrogen succinate and 1.00 mg of anhydrous Hydrocortisone basis. All excipients (bulking agent, buffer agent and pH adjuster) comply with the Ph Eur. The qualitative and quantitative composition of the freeze-dried vial is provided.

Glucose solution (for reconstitution)

The formulation contains 45 mg of glucose monohydrate and water for injection. Both excipients comply with the Ph Eur. The qualitative and quantitative composition of the glucose solution vial is provided.

Composition of the drug product after reconstitution

The qualitative and quantitative composition of the reconstituted solution is provided.

The primary packaging materials, glass vials with 'halogenated' stoppers, are sufficiently described in this section. The vial adapters are mentioned as well.

Pharmaceutical development

The pharmaceutical composition of this drug product is based on a 'reference product', marketed in France, 'Hydrocortisone Upjohn 100 mg, preparation for injection'.

The reference product includes Hydrocortisone succinate as sodium salt and the quantity is expressed as 100 mg hydrocortisone base. Excipients include monosodium phosphate monohydrate, disodium phosphate anhydrous, sodium hydroxide and water for injections.

The pharmaceutical form is powder and solvent for injection. Whereas the solvent of the reference product is water for injection, of a volume of 2 ml. Further dilution is an optional case for the reference product for infusion: Using sodium glucoside or sodium chloride infusion solutions. The use of a glucose solution for infusion is restricted to a maximum of four hours.

The main difference between the reference product and the test product is that trehalose is missing in the reference product. Furthermore, based on the indication of the reference product, the concentration of the reconstituted injection is 50 mg/ml.

For the clinical study (PREMILOC clinical trial), the reference product was used. First, the reference product was diluted with 2 ml of the WFI (50 mg/ml concentration) and then further diluted with 50 ml

of a glucose solution (standard 5% glucose solutions). This results in a concentration of an equivalent of 1 mg Hydrocortisone base. Due to the high dilution (factor 100), the amount of the "phosphate bulking agents" is decreased by a factor of 50, in comparison with the test product. Further, based on information provided and now included in the dossier, the osmolality of this solution is slightly hypo-osmolar, and less than that of the test product, where iso-osmolarity is aimed.

Following a request from the CHMP, the use of a 'non-standard' solution of glucose for the test product, instead of using standard solutions of 5% (w/v) has been justified. During clinical studies (PREMILOC) a standard glucose solution is used, in addition to 2 ml of WFI, for dilution. The use of a standard glucose solution of 5%, would result in theory in a slightly hyper -osmolar solution prior to administration.
With respect to the glucose solution proposed for the test product, increase of the pH (other than stated in the BP monograph 'glucose solution') is now tightened and justified by the data provided.

The solubility of various active substances is provided:

'Hydrocortisone hydrogen succinate', is practically insoluble in water.

'Hydrocortisone sodium succinate', is the water soluble form prepared from hydrocortisone hydrogen succinate with the aid of a suitable alkali (sodium hydroxide).

'Hydrocortisone base', is practically insoluble in water.

With respect to in-situ formation, the drug product as given to the patient complies with the BP preparation monograph 'Hydrocortisone sodium succinate for injection' as the definition of this monograph state '*sterile material prepared from hydrocortisone hydrogen succinate with the aid of a suitable alkali*'.

During pharmaceutical development, quality target product profiles (QTPP) are provided for the freeze-dried product and the glucose solution, and safety and efficacy are taken into account with respect to quality characteristics. The extractable volume is not only influenced the filling weight (including overfilling) of the powder and the diluent but is as well influenced by the adapters used for reconstitution. As the 'Extractable volume' is now defined as a CQA in the reconstituted product QTPP list, this is acceptable.

The applicant mentioned that 'no overage is used in the DP'. But overfills are used by the applicant in the freeze-dried vial and for the solution for reconstitution, due to compensate losses prior to administration. Those overfills are now clearly mentioned in the dossier section 3.2.P.2.3.6, with exact amounts Freeze-dried product, prior to lyophilisation.

Furthermore, the manufacturing development section provides information that filling volumes could have a significant impact on concentration and/or final extractable volume of reconstituted drug product due to the very small volume of the product (1ml only). The applicant focused the development on the drug product to be administered to the patient (premature infants) and its final concentration/volume, which is acknowledged.

Detailed information is provided for the use of primary packaging components, vials and stoppers. Regarding to the toxicological assessment of extractable compounds on the glass vial and the halogenated stopper of the diluent and on the glass vial and the halogenated stopper of the freeze-dried Drug Product, the risk assessment strategy for the extractables mentioned seem acceptable and the study report is now provided. Vials are depyrogenated and stoppers are sterilised. In addition to the sterilisation process of the stoppers, their drying is described in the development. As water content is seen as critical quality attribute for the manufacturing process (stability aspect due to water absorption of the freeze-dried drug product) more information is now provided. The sterilisation

process leads to a stable increase of weight. Such, the water content might be stable with respect of the stoppers. Please see chapter 4.7 as well.

A vial adapter system is used for 'easy reconstitution' (co-packaged). Filters are used as mentioned in the updated specification, as well as the diameter to fit on the vial, but additional information is requested in the dossier: Name and address of the vial adapters manufacturer and the details of the sterilisation process have been included in the dossier as requested by CHMP, but it is still missed, who is responsible for the sterilisation.

Module 1 – Information relating to paediatrics state 'Healthcare professionals can use the graduated syringe of their choice to reach the required precision according to the infant's weight.' (p. 53/173). In the PDCO request, the applicant clarifies that the 1 ml syringe is not planned to be included in the applicant's package. Furthermore, the applicant explained the dose and volume for each injection:

'A product containing 1 mg of drug substance in 1 ml of solution (i.e., Applicant's preparation). Dose and volume per injection increase by a factor of 0.01 per every 20 grams (or 0.005 every 10 grams). Hence, an infant weighing 800 grams would require 0.40 ml per injection, and an infant weighing 820 grams would require 0.41 ml per injection.' It would be possible to deliver the product in 0.01 ml increments by using a 'high accuracy' 1 ml syringe which is divided into 100 segments (i.e., 1 ml divided into 0.01 ml increments).

The precision of the correct dose for administration for the premature infants is also based on the use of a correct syringe. The posology as mentioned in the SmPC is changed to: 'Dose and volume per injection increase by a factor of 0.05 ml per every 100 grams. The product should be delivered in 0.01- or 0.05-ml increments by using a standard 1 ml syringe which is divided into 100 or 20 segments (i.e., 1 ml divided into 0.01 ml or 0.05 ml increments).'

This text is updated by reviewer to (see PI document):

'Dose and volume per injection increase by a factor of 0.05 ml per every 100 g. The medicinal product should be delivered in 0.01- or 0.05-ml increments by using a standard 1 ml syringe which is divided into 100 or 20 segments (i.e. 1 ml divided into 0.01 ml or 0.05 ml increments) (see section 6.6).'

Such, the precision of the delivery is decrease from 20 grams (respectively 10 grams) to 100 grams body weight. The applicant denied delivering a syringe within the kit as originally requested by CHMP. The applicant denied as well to mention a specific type of syringe (named by brand) (MO). This is accepted by CHMP given the justification by the applicant that the product is to be administered to children hospitalized in Neonatal Intensive Care Unit (NICU) which have expertise and equipment to treat the target population.

This prerequisite, result in the following (repeated) request:

'*6.6 Special precautions for disposal and other handling…*

… For administration the following medical device for single use is needed:

• *a 1 mL sterile syringe (including a 0.05 mL or 0.01 mL mark, not included within this pack)*

The non-use of any preservative in the formulation is acknowledged. Anyhow, the section 'microbial attributes' is quite brief, but accepted as an updated discussion is provided with respect to the bioburden before filtration. The microbial limitation of bacteria and germs in the used excipients and the drug substance is sufficient to ensure the requirements of the solution before sterile filtration.

A compatibility study is provided. The applicant clarifies that the reconstitution process, does not generate additional or more degradation products and thus, not additional decrease of the drug

substance. The compatibility of the freeze-dried product with the glucose solution (in-use storage conditions and times) is discussed in chapter "stability".

3.1.3.2. Manufacture of the product and process controls

Manufacture

The freeze-dried drug product is manufactured, packaged, tested and released in France. Information complies with that of annex 5.08.
As for this authorisation two separate sterile vial adapters (reconstitution system) are co-packed with the drug product (freeze-dried powder and glucose solution for reconstitution). For these adapters, the name and address of the manufacturer/supplier now stated in section 3.2.P.7 [powder]. But as mentioned already above, the name and address of the manufacturer responsible for sterilisation process of these adapters are missing.

The applicant provides a batch formula for the size of a batch. This batch size complies with the batch size of batches provided for process validation and batch analysis. But in addition to the volume, the number of vials (theoretical) should be mentioned. The number of theoretical vials is provided and included in the dossier section 3.2.P.3.2. A statement should be provided with respect to the number of theoretical vials, and this calculation should be traceable mentioned in the dossier. The yield of batches should be mentioned, as well.

As IPCs of the manufacturing process are based on weights, e.g. filling weight after filling, the density of the solution and the weight of solution is mentioned in the batch formula. Further, nitrogen is now added to the batch formula table as a foot note.

The use of 'Qs' should be avoided, but the correct range is included in the batch formula. Based on process validation data, the ranges for pH adjuster are quite broad and a more realistic range is awaited.

The manufacturing process can be divided in compounding, clarifying filtration and storage, sterilizing filtration and storage, and filling (pre-stoppering) followed by lyophilisation. The final steps are crimping (stoppering) and labelling. During compounding and following storage 'single use systems' or 'single use bags' are used. For life-cycle aspects these bags are now described as equipment, stating size and precise name.

Some editorial updates are requested, but not all changes are accepted. The name of the filter system should be reintroduced. Holding times (and conditions) are established conditions and now included in section 3.2.P.3.3.

pH is a critical quality attribute. The process is using higher pH for dissolution (in-situ formation of a salt) of the drug substance, and then the pH is decreased due to stability reasons. All pH determinations (for compounding (API dissolution), after solution and for the final solution) are mentioned as IPCs in the dossier. Corresponding ranges of the pH are now acceptable.

Process controls

This section includes information on all IPCs, all defined as critical process parameters (CPPs). This section is now acceptable in details, to mimic the current process.

The pH dependent solubility, as mentioned before, require precise adjustment during manufacturing, which is now acceptable.

Filling weight is mentioned as IPC. Anyhow, based on the information provided and which are now clearer for assessment, the IPC "weighing range" needs some tightening.

Intermediates are still not defined as those, and update is requested. The process shows several intermediates, including their storage. Intermediate specifications should be included in section 3.2.P.3.4.

Process validation / verification

The applicant mentioned that three '*consecutive*' batches are used for studying process validation. In detail the applicant describes that 3 validation batches have been retained for the drug product manufacturing process validation exercise. Batches have been rejected due to staff or manufacturing incidents - this information is noticed. The withdrawal of the three batches is clarified in detail. There have been exist personal and technical obstacles, which clarifies the issue sufficiently.

Process validation update now includes information with respect to: Details of the weighed amounts of the drug substance and excipients, as well as the used amounts of sodium hydroxide and two times the amount of phosphoric acid. Detailed information is now shared with respect to pH determinations (IPCs). Request on holding time is sufficiently clarified.

Excipients

All excipients used for the final drug product, including processing aids, and those used for the reconstituted solution before administration, are mentioned in Ph. Eur.

Additional tests are performed (e.g. TAMC/TYMC, endotoxin limits).

3.1.3.3. Product specification (s)

Specifications

The finished product release specifications include appropriate tests for this kind of dosage form: identification (UPLC-UV), characters (appearance, clarity and coloration of reconstituted solution) (Ph. Eur.), physical-chemical tests (water content, pH of the reconstituted solution with water, osmolality of the reconstituted solution with water, subvisible particles of the reconstituted solution with water and visible particles of the reconstituted solution with water (Ph. Eur.), filling weight per vial), content of hydrocortisone (UPLC-UV), hydrocortisone free (anhydrous hydrocortisone) (UPLC-UV), related substances (UPLC-UV), uniformity of dosage unit by mass variation (Ph. Eur.), and microbiological tests (sterility, bacterial endotoxins) (Ph.Eur.).

The current release and shelf-life specifications follow, in general, the requirements of the Ph. Eur. monograph 'Parenteralia' (0520), the Ph. Eur. general text '' (5.10), which is linked to the general monograph 'Substances for pharmaceutical use' (2024). Used methods comply with Ph. Eur. or are in-house methods. In-house methods are only used for the parameters 'Identification', 'Appearance' and 'Assay (including related substances)'.

There are some observations made by the CHMP with respect to parameters of the release and shelf-life specification which need clarification and/or updates:

The parameter 'Assay – Total hydrocortisone (mg/vial) – (%/theory)' is a determination of assay based on the filled amount of drug product per vial. Instead, the determination of assay should be a result of drug substance in a specific amount of drug product, whereas the last-mentioned amount should be weighed before use in assay determination. The unit for assay should be 'mg/g'. The term 'assay' should not be mixed with 'filling weight'. Both aspects are relevant for the drug product specification, but assay results are the amount of drug substance in a defined (weighed) amount of drug substance.

The assay 'total hydrocortisone', which is the sum of all pro-drugs (hydrocortisone {sodium} hydrogen succinate, hydrocortisone-21-hemisuccinate and free hydrocortisone), is acceptable. Note: Hydrocortisone-21-hemisuccinate and free hydrocortisone are degradants of the active substance. This is clearly understood, but the analytical method and its expression is not acceptable. It is regarded as feasible to weigh the vial (and stopper) before and after withdrawal of the cake (after drying), and to express the assay on weight. This a normal operating procedure applied for other authorised products.

The filling weight of each vial needs to be included with an appropriate limit range. The IPC filling weight before lyophilisation is not supported to be addressed in the drug product specification.

The parameter 'Uniformity of dosage unit by mass variation (%/stated content)' is stated to be determined in accordance with the Ph. Eur. 2.9.40. This would be acceptable.

Non-testing of the parameter 'reconstitution time' is justified by the applicant due to rapid dissolution (< 1min). ICH Q6A guideline would accept skip testing or omitting of this test. This is acceptable.

With respect to the limitation of assay, related substances, water, pH and osmolality, the following is mentioned here:

The limitation of assay (the sum of all three substances hydrocortisone {sodium} hydrogen succinate, hydrocortionse-21-hemisucccinate and free hydrocortisone), should be 95 – 105% for release. For shelf-life this range of 95 – 105% should be also used if not otherwise justified. A justification of widening the shelf-life range could only be based on stability results**).**

The maximum daily dose of hydrocortisone hydrogen succinate applied by this drug product is roughly 2 mg (please see evaluation in chapter 3.4). Thresholds are therefore 0.1% (RT), 0.5% (IT) and 1.0% (QT). It is mentioned here for the convenience of the reader that higher doses, which are based on a higher body weight of the preterm infants born, do not change the thresholds until more than 4 mg is given as a daily amount, which would be based on an unrealistic body weight of 4 kg for preterm infants born. SmPC cited: There is no relevant use of Hydrocortisone Aguettant in other subset of the paediatric population (above 28 weeks of gestation) in the indication of prevention of bronchopulmonary dysplasia.

Due to the before mentioned thresholds, the specification includes two impurity parameters. The limit for unknown impurities, not more than 0.5%, complies with the identification threshold mentioned before.

Hydrocortisone (free), as a known impurity, is above the IT, but as well above the QT. A limitation above the QT is possible if this impurity is 'qualified' (toxicological aspect). A qualification is possible by a monograph, and the BP monograph accepts amounts of this impurity by '7%'. A justification for the release limit is based on found values at release. The EB batch is not accepted by the assessor to justify this limit. Based on release data the limit for free hydrocortisone should be tightened.
The shelf-life limit for free hydrocortisone is now tightened. No further questions raised on this. NB: {free} hydrocortisone is the active metabolite of the drug substance. As the assay should be stated per mg of the final drug product, impurities, as well as 'free hydrocortisone' should be referenced as percentage of the drug substance (which is the sum of three substances, including free hydrocortisone). The use of a theoretical filling volume of the solution prior to lyophilisation is not accepted.

Total impurities limitation is based by the applicant on the current limitation of the Ph. Eur. monograph of the drug substance (NMT 0.75%). This sounds appropriate but is not accepted as the drug product specification focused on degradation products only, whereas the drug substance specifications take also into account synthesis by-products. For release further tightening is awaited as the proposed limit does not mimic found values. For shelf-life the limitation is still not accepted, as temperature storage

conditions should be tightened and the corresponding found values under 25°C (and 30°C) are quite low. As in-use stability results awaited at the end of shelf-life of the drug product, which might affect the found values, 'limitation of total impurities for shelf-life' is pending.

The tightened water content (shelf-life specification) is justified by the applicant due to acceptance of other parameters (e.g. impurities, in particular free-hydrocortisone). Due to the information given, which are in accordance with previous observations made by the assessor, the applicant is requested to restrict storage conditions for the drug product (powder). Maximum water content should be tightened according to the maximum level found under long-term conditions within the proposed shelf-life.

The applicant takes the option to tighten the upper pH limit.

The applicant is therefore requested, to provide data of the powder (diluted with water) and the diluent, as well as the reconstituted solution show its stability or acceptance of higher pH.
It is mentioned here to avoid any misunderstandings that any specified range of the freeze-dried product, does not justify the pH of the reconstituted solution (with glucose) stated in the SmPC (6.5 – 7.8).

Osmolality range is justified by data.

The limit of endotoxins is acceptable. The updated justification located in section 3.2.P.5.6 clarifies the limitation of endotoxins. The endotoxin limitation takes both vials into account and guarantees an acceptable low amount of endotoxins in the reconstituted drug product, prior to administration.

Finally, a risk assessment of nitrosamines is now provided in section 3.2.P.5.5 (powder). In short, the risk assessment is sufficient in detail and concludes that there is no risk of presence of nitrosamines in the freeze-dried drug product. One detail is mentioned here for the reader: As DMF is used in the drug substance synthesis and water (for injection) might contain small amounts of nitrite (can lead to formation of nitrosamines), test on three commercial batches is introduced. No nitrosamines are detected.

Analytical procedures and reference standards

Detailed information is provided for in-house methods (identification, assay and impurities). Additional data are provided for analytical methods like sterility of the solution (by membrane filtration) and bacterial endotoxins test (method D).

As already mentioned in the section before, it is bewailed that the assay is based on "per vial", instead of a (weighed) amount of the drug product. A change with respect to sampling (weighing of the drug product) is requested. As in-use data are determined, the applicant is requested to describe the sampling of the reconstituted solution and include this information in section 3.2.P.5.2. (MO)

The calculation formula of free hydrocortisone mentioned a coefficient, which is referred as theoretical target concentration in the sample solution anhydrous hydrocortisone base per ml. This coefficient is based on the vial fill volume (before lyophilisation). Reference on the theoretical filling volume (prior to lyophilisation) is not accepted. Instead, a weighing of the drug product before impurity determination is required. The amount of free hydrocortisone in the drug product should be expressed in percent, in relation to the assay of hydrocortisone {sodium} hydrogen succinate.

The method for assay and related substances is validated for repeatability and intermediate precision. No further questions on this.

Batch analysis

Three commercial batches are provided. These batches are not consecutive, but this issue has been clarified by the applicant and the MO raised at day 120 is resolved These batches show compliance with the proposed specification. There are still some points to change or to clarify, as the 'filling weight', 'assay units', and many more. Retrospective update of release batch data is not commonly asked within procedures for marketing authorisation.

Container closure

The freeze-dried product is packed into a 2 ml glass vial, enclosed with an halogenated rubber stopper. Not in contact with the drug product, but part of the packaging of the freeze-dried product, is a white aluminium capsule.

The choice of glass vials is justified. The use of clear glass vials is supported for this type of product. The sensitivity of the drug substance to light is of minor relevance, as short-term exposure of light can be tolerated for the freeze-dried product, as well for the drug product in solution. Corresponding information of the stability of the drug product (before lyophilisation) is shown without protection from light for a maximum of 6 hours. Drawings, a specification and a certificate of the applicant, is provided. Information given is sufficient.

The halogenated rubber stoppers are compliant with the Ph. Eur. monograph 3.2.9. Acceptable drawings, a specification and a certificate of the applicant and the supplier is provided.

The water content of the halogenated rubber stopper might be a critical quality attribute. The water content after sterilisation is stable. No further questions raised on this.

As both vials (powder and solution) are packed as a unit, it is easy to control completeness of the packaging unit, as the capsule of the freeze-dried vial is white, and the capsule of the glucose solution is blue.

Vial adapters

The two vial adapters are identical and fit perfectly on the vials. Pictures and drawings are provided. An updated specification of the vial adapter and analytical results are provided, including details of the filter and the diameter. The adapters are made of polycarbonate and the blister material, primary packaging material, is made of glycolyzed polyethylene terephthalate (PETG) - Ph. Eur. monograph exists for this substance. In addition, for easy use, the hollow spike is siliconized. For the 'silicone' and the 'solvent of the silicone' CoAs are provided. A statement on the regulatory information for the silicone is provided and demonstrate compliance with the Ph. Eur. monograph Dimeticone and general monograph Silicone oil used as lubricant (3.1.8). The composition of the vial adapters is now included in section 3.2.P.7 (powder) and two materials are named: polycarbonate, and the filter is made of HDPE. This composition table is not part of the specification, but this is accepted.

The filters in the adapters are made of high density polyethylene (HD-PE) resin.

3.1.3.4. Stability of the product

Table 2: Major stability studies

Temp °C, RH %	n batches x months	Batch size	Package
25 °C / 60% RH	2 batches, 12 months 1 batch, 18 months	Production scale	Intended for marketing
30 °C / 65% RH	2 batches, 12 months 1 batch, 18 months	Production scale	Intended for marketing

40 °C / 75% RH	3 batches, 6 months	Production scale	Intended for marketing

Furthermore, photostability studies are provided for one batch, the age of 3 months.

In-use stability results are provided for 4 hours, after reconstitution with glucose solution of fresh product and studies will be provided with aged batches (24 month and 36 months). It is mentioned here as an important information that in-use stability studies do not test (and will not test) sterility.

The proposed shelf-life of 24 months might be acceptable on the current guidance, but restriction of the temperature is now requested.

In-use stability studies are awaited on aged batches. Based on data in-use of 4 hours is under evaluation.

Due to the observed stability results under accelerated storage conditions, the applicant is requested to include a statement on storage conditions (e.g. **do not store above 30°C**).

The applicant is requested to discuss degradation of {free} hydrocortisone, and the applicant is also requested to discuss the possibility of its insolubility in the reconstituted solution prior to administration.

The gap in mass balance is not sufficiently discussed and a deep discussion, including data should be provided.

If not sufficiently justified, the acceptance criteria for total assay should be tightened in accordance with the release limit (95 – 105%) (MO).

Finally, to avoid any inconvenience for the applicant, as mentioned before, the current presentation of 'total hydrocortisone, per vial' is not accepted. This should be taken into account for future presentation of results.

Solvent

3.1.3.5. Description of the product and pharmaceutical development

Description of the product

The qualitative and quantitative composition of the reconstitution diluent is provided.

3.1.3.6. Manufacture of the product and process controls

Manufacture

The drug product manufacturer is responsible for manufacture and primary/secondary packaging, QC testing, as well as batch release. This information complies with that of annex 5.08.

The applicant provides a batch formula for the size of a batch. This batch size complies with the batch size of batches provided for process validation and batch analysis. The number of vials (theoretical) have been defined

The manufacturing process can be divided in compounding, clarifying filtration, sterile filtration, filling and stoppering (incl. crimping), followed by labelling.

A brief overview of the used equipment is given. "Single use systems' or 'single use bags' are used. Corresponding brand names are given, but the name of the filter system should be reintroduced.

With respect to holding times of the solutions in the compounding/storage tanks and processing time during filling are established conditions, and these conditions are now part of the manufacturing description in section 3.2.P.3.3.

Process controls

This section includes information on four IPCs, all defined as critical process parameters (CPPs).

Filling weight is mentioned as IPC. Tightening of the IPC is required.

Two intermediates are mentioned in the current description of the manufacturing process – after compounding and after clarifying filtration. Both solutions are expected to be intermediates and specifications are awaited. An intermediate product is defined as partly processed material that must undergo further processing steps before it becomes bulk product e.g. solution prior to filling. Thus, the solution of step 2 (before sterile filtration and filling) should be defined as an intermediate. Corresponding update of section 3.2.P.3.4 is waited. A specification of this intermediate is requested, but IPC can be used for most of the parameters.

Process validation / verification

The applicant confirms that batches used in the process and process validation have been consecutive. With respect to the guideline on process validation for finished products, the product to be authorised is defined as non-standard, as the method used for sterilisation (by filtration) is a non-standardised method.

Just to be noticed here, the filling volume of vials is changed between the first two validation batches and the last one.

The process validation step of compounding is mentioned now the weighing of components.

Holding and processing times are mixed in a non-acceptable manner. The holding time of the 'compounded solution before clarifying filtration' and the holding time of the 'clarified solution before sterile filtration' are yet mentioned in section 3.2.P.3.3.

Leachable studies mention one organic compound and two elemental impurities are determined. The maximum daily exposure of these components is far below the ICH limit of 120 µg/day (less than lifetime approach, < 1 months).

Excipients

All excipients and processing aids are mentioned in the Ph. Eur., and these excipients comply with the corresponding monographs. No questions raised on this chapter.

3.1.3.7. Product specification, analytical procedures, batch analysis

Specifications

The finished product release specifications include appropriate tests for this kind of dosage form: identification (B.P), characters (clarity and coloration) (Ph, Eur.), physico-chemical tests (pH and osmolality (Ph. Eur.), subvisible particles and visible particles (Ph. Eur), filling weight per vial), glucose monohydrate (B.P.), related substances (B.P.) and microbiological tests (sterility and bacterial endotoxins) (Ph.Eur.).

The current release and shelf-life specifications follow, in general, the requirements of the Ph. Eur. monograph 'Parenteralia' (0520) and the Ph. Eur. general text '' (5.10), which linked to the general monograph 'Substances for pharmaceutical use' (2024). Used methods comply with Ph. Eur. or comply with the USP and the BP.

BP monographs 'glucose infusion' can be referenced. The BP mentioned a preparation, which defines assay (95 – 105% w/v), characteristics (colourless solution, faintly yellow), identification (red precipitate or optical rotation), acidity (pH 3.5 – 6.5), 5-HMF and related substances (<0.25 absorbance), bacterial endotoxins (0.25 IU per ml).

The specification of the solvent using methods of the BP only for identification, assay and limit of 5-HMF. The limitation of pH is not in accordance with the BP monograph. The limit and the method for of 5-HMF (and related substances) determination is similar to the BP monograph. The parameters assay and limit for bacterial endotoxins are in accordance with the BP monograph.

The applicant clarifies what is meant by the limit of '≤ 0.25 AU'.

The content of glucose in the solution is ± 4.1% w/v (corresponding to 4.5% glucose monohydrate).

Instead of using the pH of 3.5 – 6.5, as stated in the British Pharmacopoeia for glucose infusion, the applicant widened the range. This widening of the upper limit is justified by the applicant. In the opinion of the applicant (see development studies), this increase of pH has no effect on the stability of the solution.
During stability there is no increase of pH observed, rather a decrease, but this might be an oscillation of the method.

The applicant mentioned that the extractable amount of this co-packed drug product includes an overfill. The parameter 'extractable volume' is now replaced by the parameter "Filling weight per vial (g)'. For this parameter a foot note describes that 'The release test of weight fill volume is performed during manufacture (In-Process control). To avoid any misunderstandings, the applicant is requested to include the target and the corresponding volume range in the specification.

The applicant justifies the osmolality range of the solvent, which would guarantee isotonic with blood (280 – 320 mOsm/L). Due to cumulative effects of limited osmolality of the powder, this is not accepted. The applicant should discuss worst case situations Based on these worst-case scenarios; an adequate specification range should be defined for the diluent. NB. Non testing of this parameter for stability is accepted, the product is quite stable and there is no sign that this parameter is stability indicating.

Analytical procedures and reference standards

Detailed information is provided for BP methods (identification, assay and impurities). Additional data are provided for analytical methods like sterility of the solution (by membrane filtration) and bacterial endotoxins test (method D). Method for the determination of impurities is shown to be selective and sufficient precise.

Batch analysis

Three commercial batches are provided and those are consecutive as mentioned before.

Container closure

The glass vials are identical with the glass vials mentioned for the freeze-dried product. The halogenated stopper is made of rubber. Not in contact with the drug product, but part of the packaging of the glucose solution, is a blue aluminium capsule.
The choice of glass vials is partly justified (please see former comment on pH increase effected by the vials).

The halogenated rubber stoppers are compliant with the Ph. Eur. monograph 3.2.9.

3.1.3.8. Stability of the product

Stability studies are carried out in accordance with the current ICH/CPMP guidelines under long term conditions (25°C/60% RH), intermediate conditions (30°C/65% RH) and accelerated conditions (40°C/75% RH). Two batches stored under long term conditions up to 18 months and one batch is stored for 12 months. All three batches are stored for 6 months under accelerated conditions. It is acknowledged that the applicant's intention is to provide data up to 36 months under long term and intermediate conditions.

The proposed shelf-life of 24 months is acceptable on the current guidance.

3.1.3.9. Post approval change management protocol(s)

N/A

3.1.3.10. Adventitious agents

N/A

3.1.3.11. GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Drug substance:

Hydrocortisone hydrogen succinate is a known chemical active substance (monographed in Ph. Eur.). A valid Certification of Suitability (CEP) is submitted as drug substance documentation.

All questions related to the drug substance are solved now.

Drug product:

Three major objections (MOs) have been raised.

One of these major objections pertains to missing critical information from the vial adapters. The name and addresses of the manufacturer/supplier and the description of the sterilisation method of the vial adapters have been provided in response to the MO raised at day 120, but the applicant should still indicate who is responsible for the sterilisation process and where it takes place. This is the reason why the MO is still not completely solved. Updated specification, including the quality of silicon oil (Ph. Eur.) is provided and acceptable.

The second major objection raised at day 120 as the batches produced for process validation are not consecutive produced has been satisfactorily addressed. Three batches are mentioned by the applicant to be retained from drug product process validation. These batches 'have been rejected due to staff or manufacturing incidents'. The withdrawal of the three batches has been clarified in detail. There have been existing personal and technical obstacles, which clarifies the issue sufficiently. No further question raised on this. In summary, this non-standard process is accepted to be validated.

The third major objection at day 120 was linked to the syringes to be used for administration. The request was partly solved as the SmPC, and other relevant texts needs to be updated:

The administration of doses below 0.05 ml should be possible (clinical acceptance to accept doses on the basis of 100 gram), the proposed SmPC text should revised to clarify that doses of 0.01 ml can be

administered correctly. The SmPC should also mention that injection the following medical devices for single use is needed: • a 1 mL sterile syringe (including a 0.05 mL or 0.01 mL mark, not included within this pack)

The question on the sampling for assay determination and limitation is still not solved. The assay should be stated in the specification as 'mg/g' and the limit should be 95 – 105%, for release and shelf-life. This issue is upgraded to MO given its importance to the benefit/risk of the product.

As mentioned in the former paragraph other concerns (OCs) have been identified regarding the finished product, its documentation and/or its manufacturing process and are still unsolved. In sum 27 OCs where the main aspects are linked to the manufacturing process and the proposed specification, including methods.

3.1.5. Overall conclusion on the quality

Three Major Objection regarding the finished product are outstanding. Therefore, the finished product documentation is still not adequate for marketing authorisation as three major objections exists.

3.2. Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of hydrocortisone are well known. As this is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

3.2.1. Pharmacology

Hydrocortisone sodium succinate is the sodium salt of hydrocortisone succinate with glucocorticoid property. It is chemically similar to the endogenous hormone cortisol. It stimulates anti-inflammatory and immunosuppressive activities in addition to exhibiting mineralocorticoid effect. Pharmacodynamic activities of hydrocortisone have been well described in the literature.

3.2.1.1. Primary pharmacodynamic studies

The numerous effects of corticosteroids are well known. They include alterations in carbohydrate, protein and lipid metabolism, maintenance of fluid and electrolyte balance. Preservation of physiological function of the cardiovascular system, immune system, kidney, skeletal, muscle, endocrine system and neurological system function. These physiological functions are also directed against any stressful and noxious stimuli and environmental changes.

Corticosteroids exert anti-inflammatory and immunosuppressive effects. Glucocorticoids (GC) exert most of their effects by binding to the glucocorticoid receptor (GR), expressed in virtually every nucleated cell of the body. The receptor – corticosteroid complex enters the cell nucleus. This complex binds to DNA determining the upregulation of anti – inflammatory mediators, inhibiting pro – inflammatory mediator expression. Synthetically derived corticosteroid analogues possess intrinsic properties to mimic and increase glucocorticosteroid or mineralocorticoid activity and potency.

The mechanism of action (MoA) of hydrocortisone is well known. It has similar MoA to that of naturally occurring cortisol.

Most of the provided information concerns the more general effects of glucocorticoids on cellular regulation and the immune system. However, the applicant does not present any clear proof-of-concept evidence support for a pharmacological mechanism of action for hydrocortisone with regard to the proposed indication of BPD. Nominal pharmacodynamics effects via aldosterone-like processes and

beta2 receptor expression increase in smooth muscles are speculated to be of relevance. More specific aspects about cellular and molecular pharmacological aspects such as affinity to target molecules – and if the expression and properties of the targets are the same or different in foetal/pre-term individuals - has not been addressed. Based on the submitted information, there is no non-clinical pharmacology support for the proposed indication.

3.2.1.2. Secondary pharmacodynamic studies

Therapeutic interests GCs have their counterpart in terms of adverse effects which are well described in literature.

Since the MoA of GCs is complex and multifaceted, undesirable effects depend on multiple factors such as the dose, regimen (extent of exposure) and type of GC, as well as sex, age and condition of the patient receiving the GC treatment.

The presence of GR in all tissues provides numerous targets for GC activity including effects in muscle cells and pancreatic beta cells. GCs may potentially induce glycaemic disturbances which may produce glucose intolerance. Corticosteroids have been shown to exert direct inhibitory action on the muscle type nicotinic acetylcholine receptor (AChR) and therefore can promote pharmacological muscle denervation.

Long term GCs therapy may decrease bone mineral density, which is of particular concern in children during bone development. The applicant considers it unlikely to occur with the proposed dose and regimen. The mechanism of effect on bone formation is however not fully understood.

3.2.1.3. Safety pharmacology programme

Non – clinical information reporting the effects of hydrocortisone on vital organ systems is limited, with the available publications dating as far back as 1950s, before the safety guidelines were established.

No non-clinical safety pharmacology studies, as per ICH S7A, were identified, and only few articles and abstracts were found by the applicant which give some insight on effects of hydrocortisone on isolated (guinea-pig, rat) heart muscle and on vascular smooth muscle in rabbit aorta in response to catecholamines.

Hydrocortisone was first shown to depress the amplitude of heartbeat in perfused guinea-pig and rat hearts, while a potentiating effect of hydrocortisone was observed in rabbit aorta (increased contractions of vascular smooth muscle in response to catecholamines) which is explained by the inhibition of the enzymatic inactivation pathway of these amines. Administered with drinking water, hydrocortisone was shown to induce, a dose – dependent manner, aortic ruptures in genetical susceptible mice to aneurysm formation and aneurysm in normal mice (Reilly 1990).

The effects of hydrocortisone on receptor density were also investigated: an increased expression of β-adrenoreceptors was shown in rat lung as well as an increased density of β2-adrenoreceptors in rat heart following daily subcutaneous hydrocortisone injection duriag 9 days more recently evidenced (Mano 1979; Mysliveck 2003).

New data has shown the effect of hydrocortisone on systemic arterial blood pressure and urinary protein excretion in a study using dogs to explore the relationship between hypertension and hypercortisolism (Schellenberg 2008). This study led to a conclusion that long-term treatment use of high doses of hydrocortisone led to significant but mild increases in systemic blood pressure and urinary protein excretion, both findings being fully reversible within 1 month following discontinuation of treatment.

The applicant listed the possibility of hydrocortisone administration generating hypoglycaemia, acute muscle weakness, and changes in bone mineral density. The relevance to the patient population (pre-term infants) remains unclear.

Hydrocortisone may have the effect of depressing the amplitude of heartbeat in perfused guinea-pig and rat hearts, a potentiating effect in rabbit aorta alternatively aortic rupture-linked aneurysm in mice. Exposure of adult dogs at 8 mg/kg hydrocortisone led to increased blood pressure and urine protein/creatinine ratio.

3.2.1.4. Pharmacodynamic drug interactions

The inflammatory, metabolic and mineralocorticoid systems interactions are the three main pharmacodynamics interactions with glucocorticoids. All are well described in the public domain.

Initially, nonclinical pharmacokinetic (PK) studies with corticosteroids were conducted in rats, mainly studying absorption and metabolism.

Absorption

In a rat study comparing various clinical administration routes, a complete absorption of 14C-hydrocortisone was achieved, as evidenced through recoveries from excrements (bile, urine, faeces) 5 days after treatment, regardless of the IV, intramuscular, sublingual or intragastric route of administration. In *in vivo* studies utilising male Sprague – Dawley rats the oral absorption was 93% (Hyde 1957; Dowty & Dietsch 1997).

The European maximum residue limit assessment report (EMEA/MRL/377/98-FINAL) states that in humans the oral bioavailability of hydrocortisone ranges from 45-80 %, and it is dose dependent. In fasted adult males, a Cmax of 199 ng/mL was attained 1 hour after an oral dose of 10 mg. In the same individuals, a Cmax of 419 ng/mL was attained 1.7 hours after an oral dose of 50 mg. The half-life for plasma elimination was reported to be in the range of 80-120 minutes. Plasma clearance was also dose-dependent and ranged from 300-500 mL/min over the dose range of 5-50 mg.

Further PK studies on hydrocortisone were conducted in human subjects to assess absolute and relative bioavailability, essentially in the context of bioequivalence evaluation of various oral formulations. the classic biexponential plasma concentration profile after IV administration was also obtained, and hydrocortisone was demonstrated to have an average of 96 % oral absolute bioavailability, achieving maximum hydrocortisone plasma levels of 300 ng/mL after 1 hour.

Studies have shown a dose-related non-linearity in the PK of hydrocortisone with increased total body clearances at higher doses. Changes in the PK of hydrocortisone at high doses may be related to drug concentration-dependent changes in the binding of hydrocortisone to plasma proteins (Toothaker & Welling 1982).

The applicant discussed further PK studies on hydrocortisone in human subjects to assess absolute and relative bioavailability (Derendorf at 1991; Johannsson et al 2009; Johannsson et 2016; Johnson et al 2018; Werumeus et al 2017).

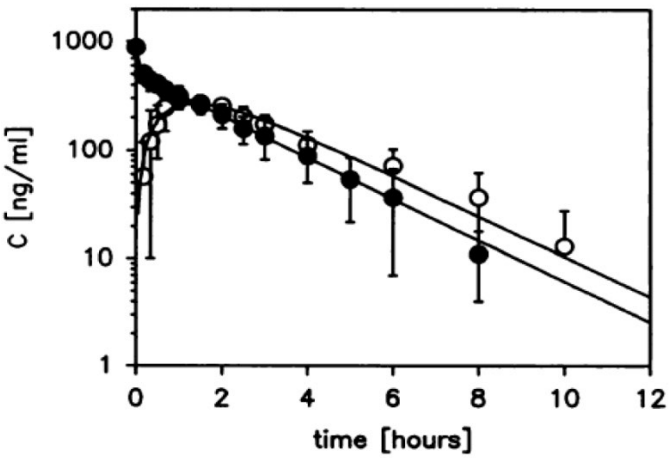


Figure 1: Plasma concentrations (mean ± SD) of hydrocortisone versus time after IV (●) and oral (°) administration of 20 mg in 8 human subjects (Derendorf et al 1991).

Table 3: Comparison of PK parameters for hydrocortisone after 20 mg IV and oral administration (Derendorf et al 1991)

Pharmacokinetic Parameters (Means and SD) for Hydrocortisone After Intravenous and Oral Administration		
	IV	PO
Non-Compartmental Analysis		
AUC [ng · h/mL]	1163 (277)	1094 (266)
CL [L/hr]	18.2 (4.2)	—
Vd_{ss} [L]	33.7 (4.6)	—
MRT [hr]	1.9 (.4)	3.2 (.5)
MAT [hr]	—	1.2 (.5)
C_{max} [ng/mL]	—	305 (57)
t_{max} [hr]	—	1.2 (.4)
BA [%]	—	95.9 (19.6)
Compartmental Analysis		
a [ng/mL]	430 (169)	—
b [ng/mL]	439 (139)	1229 (1342)
α [h^{-1}]	13.1 (11.6)	—
β [h^{-1}]	.445 (.096)	—
k_a [h^{-1}]	—	.413 (.114)
$t_{1/2}$ [hr]	1.66 (.48)	1.82 (.52)
AUC [ng · hr/mL]	1175 (285)	1162 (308)
CL [L/hr]	18.0 (4.3)	—
Vd_{ss} [L]	39.9 (7.8)	—
MRT [hr]	2.3 (.6)	3.6 (.5)
V_c [L]	23.9 (4.8)	—
Vd_{area} [L]	41.4 (9.1)	—
MAT [h]	—	1.3 (.5)
k_a [h^{-1}]	—	1.40 (.90)
C_{max} [ng/mL]	—	258 (70)
t_{max} [hr]	—	1.4 (.3)
BA [%]	—	100.5 (21.1)

Distribution

Scarce animal data for distribution are available. The applicant discussed additional published human data for completeness.

In an *in vivo* study using pregnant mice, 14C-hydrocortisone was mainly distributed to the maternal liver, bile, intestinal contents, kidney, urine and uterine luminal fluid. The adrenal cortex was slightly more radioactive that did the blood in the animals receiving corticosterone and hydrocortisone (Waddeell et al 1972).

In healthy humans, hydrocortisone displayed an apparent volume of distribution at steady state (Vdss) of 34 ± 5 L after an intravenous injection of 20 mg to 8 subjects (Derendorff 1991).

Once in the plasma of healthy humans, hydrocortisone at normal physiological concentration (400 nmol/L) is known to bind to transport proteins, mainly to the saturable corticoid binding globulin (CBG, for 80 %), with a strong affinity and specificity, and to a much lesser extent to albumin (10 %) with a lower affinity and specificity (Vezina 2014).

Therefore, the unbound and active fraction of hydrocortisone is estimated to be 5-10 % . In the context of hydrocortisone 1 mg/mL, the drug product is theorised to be dissociated rapidly into the drug substance and the excipients immediately after administration into the blood due to two factors: the fact that hydrocortisone does not react with its excipients, and due to the strong affinity of hydrocortisone for CBG and albumin (Rojek 2017).

PK of unbound hydrocortisone has been more specifically investigated in adult and paediatric populations after IV administration (Perogamvros 2011; Vezina 2014). In human neonates (n=62), treated for vasopressor-resistant hypotension with IV hydrocortisone, a morbidity often associated to adrenal insufficiency, the volume of distribution of unbound hydrocortisone, as calculated from a one compartment model, is 244 L, a lower value as compared to that reported in adults by Perogamvros and co- workers (i.e. 341.6 L) which reflects body size differences between study populations. Another difference may lie in the concentration of unbound hydrocortisone, which might be expected to be higher in the case of ill neonates experiencing hypoproteinaemia (Vezina 2014). These elements suggest the importance of dosing of corticosteroids in ill premature neonates.

Metabolism

Hydrocortisone is primarily metabolised in the liver via 11β-hydroxysteroid dehydrogenase (11 β HSD) type 1 and type 2, 5α-reductases and CYP3A4 enzymes (Walker 2001). Animal data on metabolism in rat and dog have shown that liver, kidneys and gastrointestinal tract were evidenced as important metabolism sites in these animal studies. Skin also stands as a metabolism site, as shown in a model of isolated perfused rabbit ear (Minchenko 1988; McCormick 1974; Bast & Kampffmeyer 1994).

In alloxan diabetic rats, following oral administration of 3H-hydrocortisone, the main metabolite tetrahydrocortisol was found in the liver (cytosol, microsomes, mitochondria and nuclei) in lower concentrations as compared to that in normal rat liver, while that of native hormone was increased. In the kidneys of diabetic animals, the metabolite concentration was increased and hydrocortisone was undetected, while both were found in normal animals (Minchenko 1988).

The liver is the main site of hydrocortisone metabolism with an average renal clearance of 521 mL/min basing on older studies in dogs consistent with newer finding (McCormick 1974).

Hepatic cortisol metabolism is extremely variable amongst and in the species. Abel and colleagues investigated the cortisol metabolism in liver microsomes of mice, rats, hamsters, guinea-pigs and humans after incubation with 3H-hydrocortisone for two hours (Abel et al,1992; Abel et al 1993). In rats, there are marked sex differences. In all species, hydrocortisone is converted to cortisol, but the specific cortisol metabolites that are formed differ in quantity and quality. In humans, guinea pigs, hamsters and mice, but not in rats, cortisone is observed (Abel et al 1992; Abel et al 1993).

In humans, hydrocortisone was shown to be interconvertible with the inactive metabolite cortisone, essentially in the liver where it undergoes hydroxylation then glucuro- and sulpho-conjugations

(Peterson 1955). The plasmatic half-life of hydrocortisone is about 90 minutes while its biological half-life is estimated to be 8-12 hours.

The principal metabolites of hydrocortisone (cortisol) are shown in Figure 2 (source Walker & Seckl 2001)

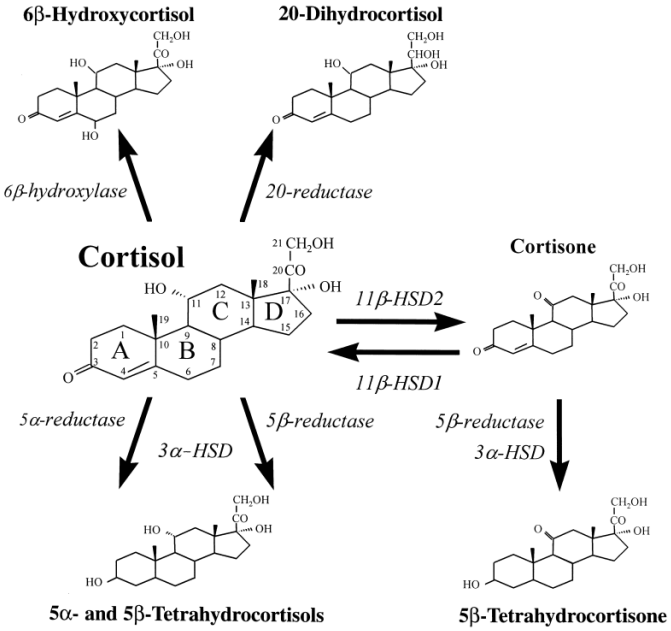


Figure 2: Hepatic metabolism of hydrocortisone / cortisol (source Walker & Seckl 2001)

11 β-HSD type 1 and 2 enzymes catalyse the interconversion of hydrocortisone, with 11 β-HSD type 2 (also expressed at a lower level in lungs) having a higher affinity for the substrate than the type 1 isoform. 5α-reductases were found to convert hydrocortisone to 5α-and 5β-tetrahydrocortisols, which represent a major part of excreted metabolites. A smaller fraction of other hydrocortisone metabolites results from the action of 6β-hydroxylase and 20-reductase, two members of the Cytochrome P450, family 3, subfamily A (CYP3A) which constitute a major part of total hepatic CYP450 population, responsible for the formation of 6β-hydroxylated products. CYP3A is highly inducible in humans by synthetic glucocorticoids. In a study using rat hepatocyte cultures, glucocorticoids were shown to stimulate synthesis of a form of cytochrome P450, P450PCN, (purified from rat liver microsomes prepared from animals treated with pregnenolone 16α-carbonitrile) for which the authors concluded of a specific glucocorticoid-responsive liver function operating through a mechanism distinct from the classic glucocorticoid pathway. In another study using a validated *in vitro* reporter gene assay system in a human hepatocyte carcinoma (HepG2) cell line, the inducibility of CYP3A4 by different concentrations of hydrocortisone showed a concentration-dependent increase in CYP3A4 activation, in the absence of any added receptor. In addition, the hydrocortisone dose-response curve was shown to fall within the physiological blood level concentration of the steroid, implicating a regulatory role for hydrocortisone in the basal level of CYP3A4 expression (Peng et al 2011; Quattrochi 2001; Schuetz 1984; El-Sankarya 2000). These mechanistic studies have potential implications for PK drug interactions involving hydrocortisone.

Excretion

Initial studies performed in 1957 have shown that after intravenous, intramuscular, sublingual or intragastric administration of 14C-hydrocortisone to rats, various excretion rates were observed (the fastest being associated to the IV route, mostly within 48 hours) although the amounts excreted were found equivalent in urine and faeces regardless of the route of administration. Around 60 % of the

radioactivity was found in the faeces, and in the urine for the remainder. Small amounts (14-20 %) of unconjugated radiometabolites were identified in the urine, while the major fraction excreted in the urine and bile consisted in water-soluble metabolites of 14C-hydrocortisone (Hyde et al., 1957).

Additional source of animal data was found in the European public MRL summary report (EMEA/MRL/377/98-Final) elaborated for hydrocortisone. After a subcutaneous administration of 0.5 mg/kg 14C-hydrocortisone in the rat, 74 to 89 % of the administered dose was recovered in the faeces within 24 hours. In the guinea-pig, a rapid excretion was also reported, mainly in urine.

In healthy human adults, after IV administration at a dose level of 20 mg, hydrocortisone was eliminated with a total body clearance of 18 L/hour and a half-life of 1.7 hour (Derendorf et al 1991). These values are consistent with earlier data shown by Peterson in 1955. This half-life disappearance value 114 min, which also stated that the 1st order-elimination rate of hydrocortisone from plasma reflects its metabolism rate, since less than 1% of administered hydrocortisone was excreted as unchanged hormone in urine.

This is also consistent with the half-life for plasma elimination reported to be in the range 80 to 120 minutes ((EMEA/MRL/377/98-Final). Plasma clearance was dose-dependent and ranged from 300 to 500 mL/min over the dose range 5 to 50 mg. In critically ill premature and full-term neonates, the clearance of unbound hydrocortisone was 20.2 L/hour and the biological half-life was 2.9 hours (Vezina 2014). Perogamvros found a 10 fold faster clearance (202.8 L/hour) and 3 fold shorter half-life (61 minutes). Hepatic clearance immaturity appears as a highly plausible reason to explain these discrepancies (Vezina 2014).

Pharmacokinetic interactions (non – clinical)

Information on drug – drug interactions is based on authorised products containing hydrocortisone. Potent CYP3A4 inducers (antibiotics like rifampicin, for example) can enhance the metabolic clearance of hydrocortisone, decrease terminal half-life and thus reduce circulating levels. Conversely, potent CYP3A4 inhibitors (ketoconazole) can inhibit the metabolism of hydrocortisone and thus increase blood levels.

Modifications of hepatic metabolism are known to constitute the major source of drug interactions.

Overall, the available non – clinical data on hydrocortisone is limited. However, this medical product has a long-standing history of use in humans (initial reports start from the 1950s). Non-clinical studies that would inform on the safety of hydrocortisone use on animals and consequently on humans are not required since hydrocortisone has a well-established use for more than 60 years.

The submitted public literature is mostly based on adult animal ADME properties and does not provide any pertinent information on developmental ADME aspects. One exception is a developmental distribution study in pregnant mice (Waddell et al., 1972), where it is reported that 14C-hydrocortisone is mainly distributed to the maternal liver, bile, intestinal contents, kidney, urine, and uterine luminal fluid. It remains unclear how the distribution is in foetal or neonatal offspring. The applicant does not provide any deeper discussion on the relevance of the adult ADME properties in a developmental context. The non-clinical pharmacokinetics dossier does not provide any specific support for the proposed indication.

3.2.2. Toxicology

No dedicated single-dose, repeated dose, reproductive and developmental toxicity, as well as genotoxicity or carcinogenicity studies have been conducted by the applicant. The applicant provided available toxicological literature.

The applicant stated that the quality and extent of the toxicity data is limited. This is principally due to the fact that the medicinal product was approved since decades, and thus the selected data come from old studies, not conducted according to current regulatory standards. Details on monitoring, scheduled observations and toxicokinetic are unavailable, as is the GLP status.

The clinically observed undesirable effects of hydrocortisone are provided from the long history of well-established use of hydrocortisone. Most reported adverse effects are associated to systemic high dosages and/or long-term use. Specific information on undesirable effects in the paediatric population receiving low doses of hydrocortisone in short treatment periods was provided by the applicant.

3.2.2.1. Single dose toxicity

In rat studies, consisting in acute intraperitoneal and subcutaneous LD50 values reported to be 150 mg/kg and greater than 1,800 mg/kg following a 7-day observation period, respectively, many deaths were reported during the second week after dosing due to infections, suggestive of the immunosuppressive action of hydrocortisone. In both mice and rats, the observed effects included reduced adrenal weights, liver damage, lung consolidation and gastrointestinal effects. The maximum dose of Hydrocortisone in BPD will be set at 2 mg/kg/24 hours; significantly below the LD50 doses discussed above.

3.2.2.2. Repeat dose toxicity

In repeated-dose toxicity studies conducted in the rabbit to exclusively investigate the potential hepatotoxicity of hydrocortisone, as is or in ester form, following daily intramuscular administrations up to 8 days, whether given at 10 or 15 mg/animal as hydrocortisone or 25 mg/animal as hydrocortisone acetate by the IM route, the glucocorticoid treatment resulted in hepatotoxicity in all treated groups.

Post-mortem examination revealed increased liver weight, focal hepatic necrosis and increased glycogen deposition when compared to control animals. After a 20 day- recovery period, the liver weights of treated animals were found comparable to controls. The No Observed Effect Level (NOEL) dose could not be established from these rabbit data. This study confirmed the liver as target organ. Hepatotoxicity is a known effect of high dose glucocorticosteroid.

3.2.2.3. Genotoxicity

Few references were identified to document the genotoxicity of hydrocortisone and hydrocortisone hemisuccinate. The data provide some questionable positive findings. Therefore, additional genotoxicity results related to other synthetic glucocorticoids were used by the applicant as supportive data.

In vitro

Ames test

This assay for gene mutation using Salmonella thyphimurium TA97a, TA98, TA100 and TA1535 strains, showed no significant dose-related increase in the number of His+ revertants per plate was observed when the hydrocortisone dose was increased from 1.0 to 1 x 103 µg/plate, either with or without metabolic activation (S9 mix). However, further increase in the concentration of the drug (5 x 103 and 1 x 104 µg/plate without S9 mix) caused a decrease in the number of His+ revertants/plate and inhibited the growth of the bacterial background lawn (Bali et al.1990).

A study in human lymphocyte cultures obtained from two healthy donors showed that hydrocortisone caused a significant increase ($p<0.01$) in the aberration (deletions and rearrangements) frequencies in this type of regulatory and standardised assay (Bali et al.1990).

In vivo

Sister – chromatid exchanges (SCE) in mouse bone marrow

Positive results were obtained in this test as shown by a significant dose-related increase in the number of SCEs as compared to the negative controls, after 24 h of intraperitoneal hydrocortisone treatment at 1 x 102, 1 x 103 and 1 x 104 µg/kg b.w. dose levels. This finding was further interpreted by the authors as an indication of interactions between hydrocortisone and DNA to produce DNA breaks during the replicative phase (Bali et al 1990). It appears very likely that these results are also artefacts of the induction of apoptosis in lymphocytes by hydrocortisone, which is technically confounded with genotoxicity (Meintieres et al 2001).

Micronucleus test

Clastogenic potential of hydrocortisone was concluded from the observation of a dose-related increase in the numbers of micronucleated polychromatic erythrocytes obtained in male mice given single intraperitoneal injection of 1 x 103, 5 x 103, 1 x 104 µg/kg hydrocortisone after a 30 h treatment duration (Bali et al 1990).

However, once again, such conclusion cannot be drawn as micronucleated cells were shown to correlate with the occurrence of apoptosis induced by glucocorticoid compounds (Meintieres et al 2001).

According to the applicant hydrocortisone cannot be considered genotoxic in this assay.

Additional *in vivo* tests

Fahmy et al (2015) published their assessment linking genotoxic and reprotoxic potential of hydrocortisone, as commercial sodium succinate.

In this study groups of five white Swiss mice were used in all experiments and were given hydrocortisone intraperitoneally (IP) at three dose levels 26, 39 and 52 mg/kg, selected as approximately equivalent therapeutic doses used in man (200, 300, 400 mg/adult, respectively).

Chromosomal aberration test in mouse bone marrow cells

A total of 500 metaphases were examined in 5 male mice per each experimental group (100 metaphase/mouse). After 24h of a single dose treatment, negative results were obtained at all three doses. However, following daily IP administrations at 26 and 52 mg/kg during 4, 7 and 14 days, a significant percentage of chromosomal aberrations in bone marrow cells was seen at the highest dose at 7 and 14 days ($p<0.05$ and $p<0.01$, respectively), while no effect was observed at 26 mg/kg even after 14 days of treatment. The authors considered this result as suggestive of genotoxic potential following long term treatment at high doses of hydrocortisone. However, some limitations are noted in this study, when compared to the standardised protocol as per OECD guideline n°475 (Mammalian Bone Marrow Chromosomal Aberration Test): the IP administration route was not justified and is not recommended as it is usually not an intended route of human exposure; there are little data available on the suitability of a repeated-dose protocol for this test; exposure of the bone marrow through plasma level determination was not done as well as general clinical observations; the number of metaphases analysed per animal is half that recommended (200 metaphases/animal).

According to the applicant, the increased chromosomal aberrations seen after a prolonged treatment at high hydrocortisone is questionable.

Dominant lethal mutation assay

In this experiment focused on germ cell mutagen identification, male mice were daily IP treated with 39 mg/kg hydrocortisone for 5 days, then individually placed with 10 untreated virgin female for a 7-

day mating period for 3 weeks Fahmy et al (2015). Frequency of dominant lethal mutation was calculated based on living foetuses per pregnant female compared to those in female controls. The results showed that the percentage of fertile mating at 1-7 and 8-14 days reduced to 50 % and 60 %, respectively, corresponding to a percentage of dominant lethal mutation of 0.23 % and 4.4 %, while no effect was recorded in the third mating interval (15- 21 days) for both treated and control groups. However, here again, some limitations in the study design are noted when compared to the standardised protocol as per OECD guideline n°478 (Rodent Dominant Lethal Test) which preclude from developing any definitive conclusion regarding the potential impact of hydrocortisone on germ cells and fertilisation: the IP route is not normally recommended and is not justified in the present experimentation; the number of females per mating interval appears underestimated to achieve at least 400 total implants allowing detection of at least a doubling in the dominant lethal frequency; only 3 weekly matings appear insufficient to evaluate all phases of spermatogenesis in the mouse which takes 7 weeks; data on toxicity and clinical signs are not reported.

Overall, hydrocortisone was not mutagenic in the Ames gene mutation test, while other *in vitro* and *in vivo* mammalian tests suggest that hydrocortisone was genotoxic. However, these positive findings are questioned by the applicant. In addition, these results conflict with the negative results obtained for another glucocorticoid in ester form: hydrocortisone aceponate, for which no evidence of mutagenicity was identified in a series of 5 studies and with the negative results of mutagenicity studies carried out with synthetic corticosteroids.

While available data on hydrocortisone supports the view that it is not mutagenic, there is some uncertainty regarding any possible clastogenicity. While there are limitations (e.g., not fully in line with OECD technical guideline recommendations) with the Fahmy et al (2015) study, it reported that high-dose IP-exposure (52 mg/kg, which can be considered a relatively high dosage in relation to the presently proposed clinical dosage of 1 mg/kg) may lead to clastogenic effects. A Dominant lethal mutation assay also reported in the Fahmy et al (2015) study indicates that hydrocortisone may reduce fertile mating events. The applicant considers that the positive genotoxic findings are not relevant. The SCE and clastogenic results are stipulated to likely be a consequence of the endogenous functionality of glucocorticoids to promote apoptosis in some cells (thereby false positives) and the studies were not fully in line with OECD technical guidelines and not GLP. It is uncertain if and how these effects in the Dominant lethal mutation assay - potential clastogenic effects in germ cells - translate to the direct neonate exposure in the proposed BPD indication.

It is agreed that, overall, it is unlikely that hydrocortisone is a mutagen and that the data currently available on clastogenicity is not sufficient to support a clastogenic concern.

3.2.2.4. Carcinogenicity

No carcinogenicity studies, as per ICH S1A (1995) and ICH S1B (1997) guidelines, on the effect of hydrocortisone have been identified.

In an abstract presenting an old life span study in rats (Schmähl et al., 1976), various chemicals, including hydrocortisone, were tested for their potential influence on incidence and induction periods of tumours in rats chronically exposed to a known carcinogen. Hydrocortisone was shown to have no effect on tumour incidences. No details were available for this published study.

The initially proposed SmPC section 5.3 text stated that "*Hydrocortisone did not increase tumour incidences in male and female rats during a limited 2-year carcinogenicity study*". While it is agreed that the exposure duration does not require an experimental carcinogenicity assessment, if such specific information is to be included in the SmPC, supportive studies should be provided for that statement. Therefore, the SmPC section 5.3 text need to be altered, and if information on

carcinogenicity is to be included, study support should be provided for that statement. In their responses, the applicant proposed to remove the mention of the study. However, in the current text included in SmPC section 5.3, there are claims about absence of tumours. Therefore, the following statement 'Hydrocortisone did not increase tumour incidences in male and female rats' still requires some evidential support (OC).

3.2.2.5. Reproductive and developmental toxicity

The applicant provided an overview of the fertility, embryo-foetal development, pre- and postnatal development studies conducted with hydrocortisone.

The earliest age for which foetal GR expression has been reported in the rat is gestational day (GD) GD9.5. There are a number of other potential sites at which GR over-stimulation could affect the programming of physiology and behaviour in the offspring. In particular, hydrocortisone could have effects on foetal development by affecting placental function, as GRs are expressed in the placenta early in gestation and increase thereafter. Given prenatally, hydrocortisone may induce long-term changes in the offspring.

Fertility

The effects of hydrocortisone on testicular tissues were tested in rats (Elshennawy et al 2011). Clear effects of hydrocortisone on testicular structure and ultrastructure when compared to controls, including degenerated changes of germ cells, Sertoli cells and Leydig cells. Tissues from hydrocortisone succinate- treated animals displayed several histopathological and ultrastructural changes such as a thickened tunica surrounding deformed seminiferous tubules, shrinkage and detachment of Sertoli cells from an irregular basal lamina in addition to necrotic Leydig cells, which are known to play a crucial role in fertility regulation through testosterone secretion, and with infiltration on the interstitial tissues. An important impact on spermatid differentiation was evidenced through absence of elongated spermatids and spermatozoa in the seminiferous tubules, indicating a disruption of spermatogenesis at the stage of rounded spermatids. All these findings highlight the potential of hydrocortisone to impair many cell (Sertoli, Leydig, germ cells and spermatogonia) development and their interaction, which may reflect on their functions essential for spermatogenesis.

No fertility data in female rats were identified.

It is agreed that hydrocortisone shows signs of being a reproductive toxicant but considering the proposed indication and the focus on pre-term infants, the fertility studies are considered of lesser relevance.

Embryo-foetal development

The potential of 3 glucocorticoids, including hydrocortisone, to induce cleft palate in the offspring was investigated in pregnant A/Jax mice following daily intramuscular administrations (Pinsky 1965). Hydrocortisone, 4 mg per day, was given to mice from day 11 to day 14 of gestation (middle period of gestation) and was compared to prednisolone (1 mg) and dexamethasone (0.15 mg). The frequency of cleft palate obtained with the 3 corticoids was 18 % (hydrocortisone), 77 % (prednisolone) and 100 % (dexamethasone). All these corticoids are potent teratogens, whose variable severity may be explained by differences in their metabolism occurring in the placenta.

The effects of hydrocortisone on the lung cell number following a single intramuscular injection in rabbit foetuses were assessed in an old study (Kotas 1974). *In utero* treatment used 2 mg hydrocortisone, administered on gestational day 24. Reduced lung and body weights were recorded for hydrocortisone-treated foetuses. In addition, a decreased number of lung cells, as measured through DNA content per lung, was observed in comparison to controls. Full recovery of body weight was

obtained within 30 days after birth with adequate nutrition, and the inhibition of lung cell number was reversed as evidenced by lung DNA content measured at necropsy, which return to control values.

An additional rabbit study was identified aiming to investigate the potential of glucocorticoids to induce polycystic kidney disease through foetal exposure (Crocker 1991). No evidence of polycystic kidneys was seen in the offspring of the treated animals injected before gestation day 11, when compared to kidneys in controls. However, a cystic kidney disease was observed in the remaining animals with a highest prevalence after injection on day 12 (50.8 %) and on day 17 (34.3 %). This finding suggests kidney as a target organ for hydrocortisone in foetal rabbits when administered on critical period of organ development.

The effects of chronic low-dose maternal hydrocortisone infusion on foetal growth, blood pressure metabolism and endocrine status in late gestation were studied in catheterised foetal sheep (Jensen 2002). Hydrocortisone was infused for 10 days vs saline (80 mg per day). The treatment was found to reduce foetal growth rate by 30 %, to increase foetal heart weight by 15 % relative to body weight through increased left and right ventricular wall thickness, and to reduce the spleen and placental weights by 30 % and 25 % respectively. The process by which the maternal cortisol infusion affects directly or indirectly the foetus is unclear. Indirect mechanism may include altered maternal metabolism or endocrine status, and/or altered placental structure and function.

It is agreed that similar to other glucocorticoids, hydrocortisone is a likely teratogen - but standard teratology studies with their focus on exposure during organogenesis are not the most relevant study designs for this proposed indication.

Among the reported EFD-like studies from public literature, the rabbit study by Kotas et al. (1974), the mouse study by Crocker & Ogborn (1991) and the sheep study by Jensen et al. (2002) were arguably the most interesting/relevant for the proposed indication. The rabbit study indicated that Gd24 rabbit foetal exposure to 2 mg hydrocortisone caused a reduction of lung cells (although the number of cells seemed to recover at PND30) whereas the mouse study indicates that foetal mice were more likely to develop cystic kidney disease traits after exposure to 250 mg/kg after Gd12 (but not before). The foetal sheep study by Jensen et al. (2002) at 80 mg hydrocortisone per day between GD119 and GD128 reported a reduction in foetal growth rate (30%) and increased foetal heart weight (15%).

Peri- and post-natal development

Effects of prenatal hydrocortisone exposure in the last period of pregnancy and its later repercussions on the fertility and sexual behaviour in male rats was studied by Pereira et al (2003). Pregnant Wistar rats were treated subcutaneously with hydrocortisone acetate at 1.5 mg/kg bw/day on GD17 to GD19. A decreased body weight was observed in the male offspring but no alteration in the anogenital distance. As adults, reduction in body weight, plasma testosterone levels and seminal-vesicle wet weight without secretion were observed. There was no alteration in the wet weights of the testes, epididymis and seminal vesicle with secretion. Males were able to mate with normal females, which became pregnant, but the number of post-implantation losses was increased. The results indicate that exposure to hydrocortisone in the later stages of pregnancy may have a long-term effect on the fertility and sexual behaviour of male rats, suggesting an incomplete masculinisation and defeminisation of the central nervous system.

A similar study was conducted in the same laboratory in female rats (Piffer et al 2004). There were no signs of maternal toxicity during the last period of pregnancy. Reduction in adrenal wet mass and plasma corticosterone levels were observed immediately after delivery in both treated mothers and their respective pups, which may indicate impairment of the HPA axis. These results indicate that the use of hydrocortisone at a dose that apparently does not endanger the neonate led to undesirable

effects in the adult reproductive phase, resulting in later deleterious alteration of the reproductive physiology in female rats.

In studies on early hydrocortisone treatment in rats to study potential effects on the development of the external granular layer (EGL) in terms of cell acquisition and differentiation, EGL being a secondary germinal zone present on the surface of the developing cerebellar cortex the total numbers of all post-natal formed interneurons were decreased by the hormonal treatment, mostly in the outer molecular layer. The inhibition of cell proliferation in the cerebellum during the hormonal treatment was also shown to induce morphological consequences which outlast the treatment period, suggesting a use of glucocorticoids at low dose in the neonatal rat so as to allow normal neurogenesis (Bohn et al 1978).

Effect of hydrocortisone on neonatal rat pancreas (Werlin 1982) demonstrated that growth and secretory capacity of the new-born pancreas are under the control of both glucocorticoids which caused precocious maturation of secretory function.

Overall, the rat studies by Pereira et al (2003) and Piffer et al (2004) report the hydrocortisone effects of a short foetal exposure (maternal exposure at 1.5 mg/kg bw/day between GD17-GD19, shortly before partus) on the post-partus offspring. The focus of the studies was on more long-term hormonal effects in relation to sexual maturation and reproduction, and the endpoints explored did not provide many insights on more immediate target organs and effects.

Some of the studies were classified as PPND but as the exposure setups were direct exposure of pups rather than via maternal *in-utero* or lactation exposure, thus these studies are more similar to juvenile toxicity studies. Among the reported adverse effects, direct exposure of offspring to hydrocortisone directly after birth (PND1 and forward) were reported to generate developmental neurotoxicity effects in the rat EGL at 200 ug (Bohn et al., 1978) and pancreatic weight and function at 2.5 to 10ug/kg (Werlin et al., 1982). Some other changes – more difficult to interpret - were in kidney and intestines.

Upon CHMP's request, the SmPC section 4.6 texts were updated in line with the intended indication/patient population. Nevertheless, issues remain to be addressed for SmPC section 5.3 (OC).

3.2.2.6. Local tolerance

No local tolerance studies have been conducted nor are considered necessary for this product to be administered by perfusion.

3.2.2.7. Other toxicity studies

All cortisone impurities are under the reporting, identification or qualification thresholds given by the "Note for Guidance on Impurities in New Drug Products" (ICH Q3B(R2)). No other toxicity studies have been conducted nor are considered relevant.

There were several impurity-related toxicologically relevant studies submitted by the applicant.

Several extractable & leachables (E & L) studies were conducted: for the extractables from filter, for the extractable compounds on the glass vial and the rubber stopper of the diluent and for the glass vial and the rubber stopper of the freeze-dried Drug Product. See quality assessment.

Several filter E & L impurities were identified and listed.

The reported levels of the E & L impurities are acceptable as their levels fall below their maximal daily exposure. As such, no additional qualification is needed. For the extractable impurities from the glass vial and the rubber stopper of the diluent plus the glass vial and the rubber stopper of the freeze-dried Drug Product, the impurities were below the TTC and do not require additional qualification.

Upon CHMP's request, the shelf-life limit for free hydrocortisone was tightened.

The active substance is intended to be reconstituted in a solvent of glucose monohydrate (and water). As such, there is the potential for a glucose-degradation impurity, 5-Hydroxymethylfurfural (also known as 5-HMF), which can be generated through a Maillard reaction. No relevant developmental toxicity are available but a mouse 3-month general toxicity study provides a NOAEL of 94 mg/kg/day (from a National Toxicology Program [NTP] set of studies from 2010) which for the present exposure conditions is adjusted to 67 mg/kg/day. This gives for <1-month PDE of 55.83 ug/kg/day for intravenous exposure and b) a >10-years PDE of 5.58 ug/kg/day for intravenous exposure.

3.2.3. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): Hydrocortisone hydrogen succinate (or Hydrocortisone sodium succinate)					
CAS-number (if available): 2203-97-6 (or 125-04-2)					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.9			Potential PBT (~~Y~~/N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	1.9			B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	2.74	µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(~~Y~~/N)
Phase II Physical-chemical properties and fate NOT PERFORMED					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies NOT PERFORMED					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

Upon CHMP's request, the applicant provided sufficient justification as to why phase II risk assessment was not performed. Overall, it is agreed that the current ERA data do not suggest a potential risk to the environment arising from the use of hydrocortisone in BPD.

3.2.4. Discussion on non-clinical aspects

Hydrocortisone is the pharmaceutical form of the endogenous glucocorticoid, cortisol and has been used for six decades worldwide. It has well-established clinical use in indications involving both systemic and local administration. It is indicated in adults and children (including neonates) due to its anti- inflammatory and immunosuppressant properties.

The primary anti-inflammatory effect of hydrocortisone, which is relevant in BPD prophylaxis, is mediated by GR and exerted through transcription modulation of a wide range of steroid-responsive genes, leading to stimulation or inhibition of protein synthesis.

The applicant did not conduct any non-clinical studies but submitted relevant published data. This is acceptable to the CHMP.

Non-clinical pharmacology and pharmacokinetics

The non-clinical pharmacology (ncPD) and pharmacokinetics (ncPK) studies provide little or no support for the proposed indication in pre-term neonates. Most of the information derives from studies and overviews on hydrocortisone in adult animal (or human) conditions with little or no attempts to discuss the relevance for the intended pre-term neonate population. One exception is a developmental distribution ncPK study in pregnant mice (Waddell et al., 1972), where it is reported that 14C-hydrocortisone is mainly distributed to the maternal liver, bile, intestinal contents, kidney, urine, and uterine luminal fluid. But the study does not address how the distribution is in foetal or neonatal offspring.

To address the limited availability of ncPK data, human data for bioavailability, distribution and excretion were provided. Across species, hydrocortisone is bound by about 90 % to plasma protein over a wide range of concentrations and is distributed, by passive diffusion, to the liver, bile, colon and kidney. Hydrocortisone is almost completely eliminated by metabolism in the liver via 11β-hydroxysteroid dehydrogenase and CYP3A4 enzymes. The half-life for plasma elimination ranged between 80 to 120 minutes. Main metabolites, tetrahydroxycortisone and tetrahydroxycortisol, were rapidly excreted in urine. In the case of ill premature neonates, a lower circulating plasma protein concentration (such as CBG and albumin) as well as a reduced liver enzymatic battery, both expected in such population experiencing hypoproteinemia, may influence the distribution of hydrocortisone as well as its metabolism extent. Interaction with a CYP3A4 inhibitor, such as an antifungal (e.g. ketoconazole) or CYP3A4 inducer, such as antibiotics (e.g. rifampicin), may potentiate or compensate the hepatic clearance immaturity. Taken together, these potential PK changes in the targeted population suggest a careful monitoring without precluding its use for the intended indication.

Non-clinical toxicology

From a Human toxicology perspective, the main points of interests were the i) developmental effects of hydrocortisone on foetuses and neonates, and ii) the toxicological profiles of the impurities and leachables in the drug product.

Glucocorticoids are generally considered likely human teratogens, and hydrocortisone is also a known teratogen associated with cleft palate malformations. The toxicity studies of greatest relevance in this application were those that could mimic the exposure state of pre-term infants - which can be considered *in-utero* studies where the mothers stated to become exposed after organogenesis (foetal exposure) and studies where neonates are exposed directly after birth. Adult animal toxicity studies were also reported but their relevance is uncertain. Among the reported EFD-like studies from public literature, the rabbit study by Kotas et al. (1974), the mouse study by Crocker & Ogborn (1991) and the sheep study by Jensen et al. (2002) were arguably the most interesting/relevant for the proposed indication. The rabbit study indicated that Gd24 rabbit foetal exposure to 2 mg hydrocortisone caused

a reduction of lung cells (although the number of cells seemed to recover at PND30) whereas the mouse study indicates that foetal mice were more likely to develop cystic kidney disease traits after exposure to 250 mg/kg after Gd12 (but not before). The foetal sheep study by Jensen et al. (2002) at 80 mg hydrocortisone per day between GD119 and GD128 reported a reduction in foetal growth rate (30%) and increased foetal heart weight (15%). Among the reported adverse effects from direct exposure of offspring to hydrocortisone directly after birth (PND1 and until PND4 or PND5), there were reports of developmental neurotoxicity effects in the rat external granular layer (EGL; a secondary germinal zone present on the surface of the developing cerebellar cortex) at 200ug (Bohn et al., 1978) and pancreatic weight and function at 2.5 to 10ug/kg (Werlin et al., 1982). No toxicokinetic data is available that would allow the estimates of exposure margins.

Repeat-dose toxicity data are available from rabbit studies. The evaluations confirm that the liver is the major target organ as shown by increased weight, focal necrosis and increased glycogen deposition when hydrocortisone was administered (IM) at 10 or 15 mg/animal/day for 8 days. No NOEL was established.

No signal for mutagenicity was detected in the Ames test while other *in vitro* and *in vivo* mammalian tests suggest that hydrocortisone could be clastogenic. These positive findings can be explained by GC-induced lymphocyte apoptosis which can be confounded with genotoxicity in *in vitro* clastogenic assays due to DNA fragmentation occurring during apoptosis. While there are no carcinogenicity studies of hydrocortisone available, there is currently no suspicion of a carcinogenetic potential of GCs.

Besides the active substance, there is also a proportion of free hydrocortisone in the formulation (initially around 10%) which is classified as an impurity. Based on the premise of a maximum 1.6 mg/d dose (1 mg/kg with a maximum weight for preterm 24w-28w infants at 1.6 kg), the applicant calculates a daily dose of 10% x 1.6 mg/d = 160 ug/d impurity. It is considered unlikely that the free hydrocortisone generates potential safety concerns that are different or distinct from hydrocortisone hemisuccinate. The applicant tightened the shelf-life limit for free hydrocortisone to 5%, which is agreed by CHMP. In addition, the active substance is intended to be reconstituted in a solvent of glucose monohydrate (and water). As such, there is the potential for a glucose-degradation impurity, 5-Hydroxymethylfurfural or 5-HMF), which can be generated through a Maillard reaction. No relevant developmental toxicity studies are available for 5-HMF. 5-HMF is known to be a mouse carcinogen. It is not genotoxic itself but its metabolite SMF, is considered genotoxic. 5-HMF is carcinogenic in female (but not male) mice - and not in rats - but the rodent biotransformation into its metabolite is very low, making it questionable that it has a major role in the carcinogenesis. Presently, the mechanisms underlying the positive mouse results are unclear. An EFSA assessment from 2011 on 5-HMF as a flavouring agent considered it unlikely that exposure to 5-HMF generates genotoxic or carcinogenic concerns. Instead, a permitted daily exposure (PDE) estimate has been calculated for 5-HMF – which is considered a reasonable risk assessment approach. The applicant used a mouse 3-month general toxicity NOAEL of 94 mg/kg/day (from and NTP set of studies from 2010) - adjusted to PDE of 67 mg/kg/day - as the point of departure for PDE calculations. For IV-exposure, this gave a 55.83 ug/kg/day (short-term, <1 month exposure) alternatively 5.58 ug/kg/day (long-term, >10 years exposure) limit. Additionally, extractables and leachables (E & L) studies have been conducted. Most E & L impurities were below Limit of Quantification, but some organic and metallic impurities were identified. There were adequately addressed by the toxicological risk assessment.

ERA

Overall, the current ERA data do not suggest a potential risk to the environment arising from the use of hydrocortisone hydrogen succinate.

SmPC

The SmPC section 5.3 text should be more aligned to toxicological studies submitted and relevant to the proposed indication. In this context, it can also be noted that there is a note on "Hydrocortisone did not increase tumour incidences in male and female rats during a limited 2-year carcinogenicity study". While it is agreed that the exposure duration does not require an experimental carcinogenicity assessment, if such information is to be included in the SmPC, study support should be provided for that statement. The information was nominally derived from an abstract presenting an old life span study in rats by Schmähl et al. (1976) but this cannot be considered evidential support. To address the OC raised, the applicant suggested to remove the reference to the 2-year carcinogenicity study. However, there are still claims included in SmPC section 5.3 about absence of tumours. Therefore, the following statement 'Hydrocortisone did not increase tumour incidences in male and female rats' still requires evidential support (OC).

Overall, the available non-clinical studies in various species indicate that there are potential hazards with the exposing preterm neonates to hydrocortisone, but these studies are considered less representative for hazard identification than the clinical experience derived from the historical use of the more potent dexamethasone on pre-term infants (see Clinical assessment).

3.2.5. Conclusion on non-clinical aspects

Overall, there are no major non-clinical issues that affect the approval; some concerns need to be addressed.

3.3. Clinical aspects

3.3.1. Introduction

This is an application for Hydrocortisone Aguettant 1 mg/ml Powder and Solvent for Solution for Injection, in the prevention of bronchopulmonary dysplasia in preterm infants born between 24 and 28 weeks of postmenstrual age.

To support the marketing authorisation application, the applicant submitted the results of a single pivotal phase 3 study as well as literature references.

3.3.2. Exemption

In accordance with the EMA guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. The applicant claims that the minor difference in excipients does not interact with the active substance or otherwise affect the disposition of the active substance.

A physical-chemical comparative study between the two formulations (Hydrocortisone Aguettant and Reference product) has been performed to demonstrate their equivalence. Particularly, the study investigated the effect of trehalose excipient present in Hydrocortisone Aguettant formulation. The results show that both products can be considered as pharmaceutically equivalent.

Overview of clinical studies

To support the application, the applicant has submitted one single pivotal phase 3 study (PREMILOC).

3.3.3. Clinical pharmacology

3.3.3.1. Pharmacokinetics

No specific PK study was performed in neonates with hydrocortisone (HC). This is agreed as the product is administered intravenously and *in vitro* comparability between the reference medicinal product and hydrocortisone has been shown (see quality aspects).

PK data from the literature for unbound HC, the pharmacologically active moiety, were recorded in critically ill neonates and infants with vasopressor-resistant hypotension who received intravenous HC. Unbound HC clearance (CL) increased with body weight and was faster in children with an older PMA. Unbound HC CL increased sharply at 35 weeks PMA and continued to mature thereafter (Vezina 2014).

Derendorf (1991) in another study assessed the PK characteristics of oral HC in 62 critically ill neonates and infants (median gestational age 27 weeks and median postnatal age 0.7 weeks) found that population estimates for clearance and volume of distribution were 20.2 L/hr (95% CI 15.9-24.5) and 244 L (95% CI 160-328) respectively. Using the median weight and postmenstrual age of their subjects (1.2 kg and 27 weeks), the typical unbound HC clearance was 1.0 L/h with a volume of distribution of 4.2 L. This corresponded to a half-life for unbound HC of 2.9 hours. The study found that there was a sharp and continuous increase in unbound hydrocortisone clearance at 35 weeks postmenstrual age.

Interactions

The applicant has made a review of the available literature. There is limited data about drug-metabolising enzymes in preterm infants. Concomitant administration of other medicinal products requires particular attention due to uncertainty around the risk of interactions in preterm infants. The proposed SmPC reflects the uncertainty around the risk of interactions in preterm infants. Possible interactions with other medicinal products and impact on hydrocortisone are described in the SmPC.

Table 4: Important drug or substance interactions / effects with hydrocortisone

Drug Class or Type - DRUG or SUBSTANCE	Interaction / effect
Antibacterial - Isoniazid	CYP3A4 INHIBITOR Described for prednisolone: decrease in plasma concentration of isoniazide. Possible mechanism: increase in hepatic metabolism of isoniazide and decrease in corticosteroid metabolism. Need for clinical and biological monitoring
Antibiotic, Antitubercular - Rifampin	CYP3A4 INDUCER Decrease in plasma concentrations and efficacy of corticosteroids due to an increase in their hepatic metabolism because of rifampicin; *consequences may be significant in Addison patients treated with corticosteroids or in case of transplantation. Need for clinical and biological monitoring; corticosteroids dosage should be adapted during rifampicin treatment and after its termination*.
Anticoagulants (oral)	*The effect of corticosteroids on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects.* *The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.* *Possible impact of corticosteroids on the metabolism of oral anticoagulant and of coagulation factors. Haemorrhagic risk specific to the corticosteroids (digestive mucous membrane, vascular weakness) used at high dosages or for a prolonged duration (above 10 days). When the combination is justified, the monitoring should be enhanced:*

	biological monitoring on 8th day, then every 15 days during the corticosteroid treatment and after its termination.
Anticonvulsants. - Carbamazepine	CYP3A4 INDUCER (and SUBSTRATE).
Anticonvulsants. - Phenobarbital - Phenytoin	CYP3A4 INDUCERS.
Anticonvulsivants enzymatic inducers	Carbamazepine, fosphenytoïne, phenobarbital, phenytoïne, primidone. Decrease in plasma concentrations and efficacy of corticosteroids due to an increase on their hepatic metabolism by the inducer. Consequences may be important in Addison patients treated with hydrocortisone and in case of transplantation. Need for clinical and biological monitoring; corticosteroids dosage should be adapted during inducer treatment and after its termination.
Anticholinergics - Neuromuscular blockers	Corticosteroids may influence the effect of anticholinergics. 1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers Steroids have been reported to interact with neuromuscular blocking agents such as pancuronium with partial reversal of the neuromuscular block.
Anticholinesterases	*Steroids may reduce the effects of anticholinesterases in myasthenia gravis.* *Steroids may reduce the effects of anticholinesterases in myasthenia gravis.*
Antidiabetics	*Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.*
Antiemetic *- Aprepitant* *-Fosaprepitant*	*CYP3A4 INHIBITORS (and SUBSTRATES)*
Antifungals - Itraconazole -Ketoconazole	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals *- HIV-protease inhibitors*	*CYP3A4 INHIBITORS (and SUBSTRATES)* *b) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.* *2) Corticosteroids may induce the metabolism of HIV-protease inhibitors resulting in reduced plasma concentrations.*
Pharmacokinetic enhancers *-Cobicistat*	*CYP3A4 INHIBITORS*
Aromatase Inhibitors *- Aminoglutethimide*	*Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.*
Calcium Channel Blocker *- Diltiazem*	*CYP3A4 INHIBITOR (and SUBSTRATE)*
Cardiac Glycosides - Digoxin	Concurrent use of corticosteroids with cardiac glycosides may enhance the possibility of arrhythmias or digitalis toxicity associated with hypokalemia. In all patients taking any of these drug therapy combinations, serum electrolyte determinations, particularly potassium levels, should be monitored closely. Hypokalemia promoting toxic effects of digitalis. Any hypokalemia should be corrected first, and a clinic, electrolytes, and electrocardiographic monitoring should be performed
Contraceptives (oral) *- Ethinylestradiol/ Norethindrone*	*CYP3A4 INHIBITOR (and SUBSTRATE).*
Oestrogens (including oral contraceptives containing oestrogens)	*CYP3A4 INHIBITOR (and SUBSTRATE)* *Oestrogens may potentiate effects of hydrocortisone by increasing the concentration of transcortin and thus decreasing the amount of*

	hydrocortisone available to be metabolized. Dosage adjustments of hydrocortisone may be required if oestrogens are added to or withdrawn from a stable dosage regimen.
- Grapefruit juice	*CYP3A4 INHIBITOR.*
Immunosuppressant - Ciclosporin	CYP3A4 INHIBITOR (and SUBSTRATE). Even if this medicine will never be administered to extremely preterm infants, it could be used by the mother during the pregnancy. Increased activity of both ciclosporin and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use. Convulsions have been reported with concurrent use of corticosteroids and ciclosporin. Since concurrent administration of these agents results in a mutual inhibition of metabolism, it is possible that convulsions and other adverse effects associated with the individual use of either drug may be more apt to occur
Immunosuppressant *- Cyclophosphamide* *-Tacrolimus*	*CYP3A4 SUBSTRATES.*
Macrolide Antibacterial - Clarithromycin -Erythromycin	CYP3A4 INHIBITORS (and SUBSTRATES).
Macrolide Antibacterial - Troleandomycin	CYP3A4 INHIBITOR.
NSAIDs - high-dose Aspirin (acetylsalicylic acid)	1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. 2) Corticosteroids may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of corticosteroid treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity. The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication. Salicylates and non- steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids in hypothrombinaemia
Potassium Depleting Agents	When corticosteroids are administered concomitantly with potassium depleting agents (i.e., diuretics), patients should be observed closely for development of hypokalaemia. There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure. The hypokalemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced. Hypokalaemic drugs: Hypokalaemic diuretics in monotherapy or in combination, stimulating laxatives, amphotericin B IV, tetracosactide: increased risk of hypokalaemia. Kalemia monitoring and correction if needed. Hypokalaemia is a risk promoting the occurrence of heart rhythm disorders (notably torsades de pointe). It increases some medications toxicity, for example digoxin. Therefore, medications that may induce hypokalaemia are involved in many interactions. They are hypokalaemiic diuretics, in monotherapy or in combination, stimulating laxatives, corticosteroids, tetracosactide, amphotericin B (IV route).
Live Attenuated vaccines	*Risk of generalised vaccine disease, potentially deadly.*
Sultopride	*Increased risk of ventricular rhythm disorders notably torsades de pointe.*
Class Ia and class III antiarrhythmics	*Drugs responsible for torsades de pointe except sultopride (see "associations déconseillées"):* *Class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide) and class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide), some antipsychotics (thioridazine, chlorpromazine, levomepromazine, cyamemazine, sulpiride, amisulpride, tiapride, pimozide, haloperidol, droperidol, veralipride), bepridil, cisapride, diphemanil, erythromycine IV, halofantrine, lumefantrine, methadone, mizolastine, moxifloxacine, pentamidine, spiramycine IV, vincamine IV.*

	Increased risk of ventricular rhythm disorders, notably torsades de pointe. *First correct any hypokalaemia before administration of the drug and perform clinical, electrolyte and electrocardiographic monitoring.*
Insuline*, metformine, sulfamides hypoglycaemiants*	*Glycaemia increased with possibility of acidocetosis due to a decrease in glucose tolerance because of corticosteroids. The patient should be warmed and the monitoring of glycaemia and urinary monitoring should be reinforced, especially at the beginning of treatment. The dosage of the antidiabetic drug can be adapted during the corticosteroid treatment and after its termination.* The desired effects of *hypoglycaemic agents including* insulin are antagonised by corticosteroids.
Antihypertensives and diuretics	The desired effects of antihypertensives and diuretics are antagonised by corticosteroids.

3.3.3.2. Pharmacodynamics

No new PD studies were presented, and no such studies are required for this application.

The PD properties of HC are well known, since it has been studies and extensively used for the past 5 decades.

It is a naturally occurring glucocorticoid hormone of the adrenal cortex. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt- retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogues are primarily used for their anti-inflammatory effects in disorders of many organ systems.

Mechanism of action (MoA)

Infants born before 28 weeks of gestation may express relative adrenal insufficiency leading to inappropriate release of endogenous cortisol in response to stress. The deficiency in cortisol in addition to an immature hypothalamic–pituitary–adrenal axis may lead to improper regulation of metabolism and inflammatory systems thereby hindering normal adaptation to the intense stress associated with preterm conditions. Substitution of hydrocortisone hemisuccinate during the first 10 days of life is suggested to induce a pulmonary anti-inflammatory effect.

The MoA of corticosteroids in the management of BPD is based on their anti- inflammatory properties.

3.3.4. Discussion on clinical pharmacology

Pharmacokinetics

The MAA is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The chosen reference product is Hydrocortisone UPJOHN 100 mg, solution for infusion, from France. Differences compared to the reference product are changes in therapeutic indications and strength.

To support the application, the applicant has submitted one single pivotal efficacy and safety study (PREMILOC). There was no PK sampling in the PREMILOC study. The reference product (from Upjohn) was the only product used in the pivotal clinical study. The applied product has not been used in any clinical studies. The clinical trial and the to-be marketed formulations are different in nature and concentration for some excipients. No PK bridging study is considered necessary since the product is administered intravenously and *in vitro* comparability between hydrocortisone and the reference medicinal product has been shown (see quality aspects).

There has been no specific PK study performed in neonates with hydrocortisone. No PK data have been generated to support this hybrid application since hydrocortisone is well-known and has been approved

for many years. PK properties of hydrocortisone are described based on available data from other hydrocortisone hemisuccinate SmPCs. This is considered acceptable.

The SmPC sections 4.5 and 5.2 are based on available data in the currently marketed hydrocortisone hemisuccinate SmPCs. The data mainly refer to PK in adults, even if these products are indicated both in adults and children.

Upon CHMP's request, the applicant has made a review of the available literature. There is limited data about drug-metabolising enzymes in preterm infants. Concomitant administration of other medicinal products requires particular attention due to uncertainty around the risk of interactions in preterm infants.

The proposed SmPC reflects the uncertainty around the risk of interactions in preterm infants. Possible interactions with other medicinal products and impact on hydrocortisone are described in the SmPC.

Pharmacodynamics

The PD properties of HC are well known, since it has been studies and extensively used for the past 5 decades. It is a naturally occurring glucocorticoid hormone of the adrenal cortex.

The MoA of corticosteroids in the management of BPD is based on their anti- inflammatory properties. Infants born before 28 weeks of gestation may express relative adrenal insufficiency leading to inappropriate release of endogenous cortisol in response to stress. The deficiency in cortisol in addition to an immature hypothalamic–pituitary–adrenal axis may lead to improper regulation of metabolism and inflammatory systems thereby hindering normal adaptation to the intense stress associated with preterm conditions. Substitution of hydrocortisone hemisuccinate during the first 10 days of life is suggested to induce a pulmonary anti-inflammatory effect.

3.3.5. Conclusion on clinical pharmacology

Overall, no major objections are raised regarding the approval of hydrocortisone from a clinical pharmacology point of view, however a SmPC comment in section 5.2 needs to be addressed.

3.3.6. Clinical efficacy

The efficacy of hydrocortisone (HC) for prophylactic use in preterm infants born between 24 -28 weeks of post-menstrual age to prevent bronchopulmonary dysplasia (BPD) is supported by a prospective, placebo-controlled, randomised, double-blind, single pivotal phase 3 study conducted in France, the PREMILOC study. This study assessed the efficacy and safety of HC administered intravenously at a dosage of 0.5 mg / kg / 12hours for 7 days, then 0.5 mg / kg / 24hours for 3 days (slow injection after reconstitution in a final concentration of 1 mg/ml). The treatment is to be initiated as soon as possible before the 24th hour of life. Additional post-hoc analyses were performed and published.

In addition, the efficacy of HC was assessed in published studies in which treatment was initiated within 7 days of life, even within the first 48 hours of life for preventing BPD. This "early" initiation (within 7 days of life) was chosen to be consistent with the Cochrane reviews and meta-analyses that were performed. In addition, an earlier initiation is consistent with a prophylaxis strategy rather than an early treatment strategy as for selective treatment initiated in severely ill patients after 7 days of life. The main rationale supporting the prophylactic use of HC is related to low cortisol levels measured in extremely preterm infants within the first week of life and associated with an increased incidence of PDA, increased lung inflammation, and an increased incidence of BPD. These data suggest that early adrenal insufficiency also underline the previously observed association of increased lung inflammation and PDA with subsequent adverse respiratory outcome in neonates born extremely preterm.

3.3.6.1. Dose response study(ies)

No dose finding studies were conducted which is acceptable. Different doses and treatment durations are described in the literature. The chosen doses represent a low dose level which is appropriate from a safety perspective. The dose applied is roughly in accordance with the dose approved for use in the case of adrenal insufficiency in neonates.

3.3.6.2. Main study

PREMILOC - Early Low-Dose Hydrocortisone to Improve Survival without Bronchopulmonary Dysplasia in Extremely Preterm Infants: a Randomised, Double-Blind, Placebo-controlled, Multicentre Trial

Methods

Study participants

Inclusion criteria:

- Neonate with gestational age between 24+0 and 27+6 weeks of gestation* born in a context other than those specified in the exclusion criteria,
- Neonates whose parental authority holders have signed consent forms,
- Neonates whose parental authority holders are covered by a French social security system,
- Informed consent provided before inclusion and randomisation.

*The PREMILOC study was performed in premature infants born between 24 and 27 weeks of PMA. The decision not to include neonates born before 24 weeks of PMA was taken as, at the time of PREMILOC study initiation, these children were not resuscitated in France.

Exclusion criteria:

- Congenital malformation and/or heart diseases other than patent ductus arteriosus or foramen ovale
- Rupture of membranes before 22+0 weeks of amenorrhea
- Multiple pregnancy over triplets
- Newborns with birth weight < 500g
- Intra Uterine Growth Retardation with birth weight <3rd percentile for gestational age according to French-sex AUDIPOG customised curves
- Newborns with severe perinatal asphyxia (Apgar score of 0–3 for more than 5 minutes, cord blood pH of less than 7.00, or both) and expected to die shortly after birth
- Newborns with congenital malformations (birth defects or major structural abnormalities detectable prenatally) or known chromosomal aberrations

Treatments

Hydrocortisone (HC) or placebo IV (vials containing glucose 5%)

Objectives

Primary

- Reduction in neonatal mortality and occurrence of BPD

Secondary

- evaluation of the impact of hydrocortisone on neonatal mortality and respiratory morbidities

Outcomes/endpoints

Primary endpoint:

Surviving preterm infant without BPD at 36 weeks of amenorrhea termed "success"

Dead preterm infant or surviving but oxygen-dependent or dependent on any ventilation method irrespective of Fi02 at 36 weeks of amenorrhoea termed "failure".

Secondary endpoints (assessed post-hoc):

A number of different secondary endpoints were listed, differing somewhat between the applicant's CSR and the Lancet paper. Results are presented for some of these but not all. There was no predefined multiple testing procedure and thus the results should be interpreted with caution.

Examples of secondary endpoints are listed below:

- Neonatal all-cause mortality at 28 days
- Survival rate at 2 years of age
- The rate of subjects receiving invasive mechanical ventilation
- Need for PDA ligation
- Use of systemic postnatal corticosteroids (hydrocortisone or other steroids) beyond the treatment period by hydrocortisone expressed as cumulative or equivalent (doses not available in the database)
- Extubation rate at day 10 of life

Sample size

Planned: 393 subjects per group. Enrolled: 519 subjects; 255 in the HC group, 264 in the placebo group.

Randomisation and blinding (masking)

Randomisation was balanced by a block size of 4 and stratified by centre and gestational age (two strata: 24+0 to 25+6 and 26+0 to 27+6 in weeks of PMA).

The block size was not communicated to the clinicians. The block size was set to meet treatment dispensing organisation requirements in the centres.

Central randomisation (via internet) performed electronically after verification of inclusion and exclusion criteria and obtained consent. The randomisation sequence was generated electronically with nQuery (version 6.01). All infants were electronically randomised before they reached 24 completed hours of life. Infants were randomly assigned 1:1 to either HC or placebo via a central computer-generated list.

The appearance of the HC and placebo vials was strictly identical, and subject information and treatment groups were masked from all participants in the research (i.e., parents, nurses, and physicians).

A triple masking (participant, investigator, outcomes assessor) was in place.

Study drug: Lyophilisate for injection containing 100 mg of hydrocortisone sodium succinate (INN)/2 ml, (corresponding to the proprietary medicinal product HYDROCORTISONE UPJOHN 100 mg, preparation for injection) in a presentation compatible with the performance of a double-blind trial.

Placebo: Vials of lyophilisate identical in appearance to those of the drug product, in accordance with GMP of Medicinal products for Clinical trials, with a formula that guarantees the safety (same qualitative and quantitative formula as the drug product except for the absence of hydrocortisone sodium succinate, replaced by endotoxin-free mannitol).

Statistical methods

Two initial statistical analytical plans (SAPs) were provided at the time of the study, before breaking the code, one for the short-term outcomes, 36 weeks, (dated 5th January 2014) and one for the long-term outcomes, 2 years, (dated 1st July 2016). These original SAPs were designed to only provide necessary information for publication; they were not in line with requirements entailed for a MAA. Furthermore, the applicant received the database with two missing subjects, due to parents' consent withdrawal, after the acquisition of the rights to the trial database. Therefore, in addition to the 2 initial SAPs, an additional SAP was created to take into account the analyses not planned in the initial ones (for example regarding safety parameters), and to answer some requests from the PDCO related to confounding factors, included Univariate and multivariate analyses dedicated to assess the efficacy result while taking into account subjects baseline characteristics: given the nature of the study a two-way Analysis of Variance (ANOVA) was deemed more appropriate in a re-analysis. Furthermore, according to a literature review, several baseline variables (covariates) are expected to impact the main outcome (both on mortality and BPD), which implies that an important part of the overall residual variability of the endpoints is attributable to these covariates. As a consequence, adjusting for these baseline conditions was theorised to substantially improve the power of the test.

The objective of the calculation of the number of subjects required was to enable the comparison of the primary endpoint, in this case the criterion combining the development of BPD at 36 weeks +/- 3 days of amenorrhoea or death before 36 weeks +/- 3 days of amenorrhoea in the two randomisation groups. The expected percentage of deaths is 25% and that of onset of BPD of 25% on infants alive at 36 weeks +/- 3 days of amenorrhoea. In total, the percentage of expected event is 44% (out of 100 neonates, 25 will die and 19/75 surviving infants will have BPD, i.e. 44/100 events).

It was hypothesised that HC will reduce neonatal mortality from 25 to 20% and could also reduce the proportion of BPD from 25 to 18% of surviving infants at 36 weeks +/- 3 days of amenorrhoea (i.e. 14 BPD/80 surviving infants and a total of 36/100 events).

In total, a decrease in the proportion of total events from 44% to 34% was expected and therefore a success proportion of 56% in the placebo arm and 66% in the treatment arm. Setting an alpha risk =5%, beta risk =20%, in two-tailed formulation, balancing the randomisation (1:1), 393 subjects should be included per group to demonstrate an absolute difference of 10% of success in the HC group (66% of success) relative to the placebo group (56% of success), i.e. 2 years of inclusion and 4 years of study.

Descriptive analysis

The qualitative analysis is the number of patients (percentage) and the quantitative variables as the mean (Standard deviation) or median (1st – 3rd quartiles) depending on Gaussian or non – Gaussian nature of their distribution. Parametric or non – parametric tests were used depending on the nature of the variables. The test was a two tailed with a level of significance of 5%. The SAS v9.3 was used.

Sequential analyses

The statistical analysis was performed each time a group of 100 consecutive preterm infants has been assessed. It was performed on the primary criterion.

Final analysis

The final statistical analysis was to be performed according to the intention to treat principle (i.e. analysis of all patients included in the study irrespective of the treatment received) after stopping the inclusions. It was to be performed on the preterm infants included, i.e. also including those who did not participate in the triangular test during an interim analysis.

The study was initially planned to use a randomised triangular plan allowing for sequential testing of the success rate. The analysis of the primary endpoint was performed using an unadjusted $\chi 2$ test of comparison of two proportions between two independent samples (as was originally planned).

Missing data were not replaced. For the primary endpoint, it was coded as a failure to preserve the intention-to-treat analysis.

Full Analysis Set (FAS): All subjects for whom a consent to participate in the study is available.

Safety Set (SAF): All randomised subjects who received at least one dose of study medication (HCHS or placebo).

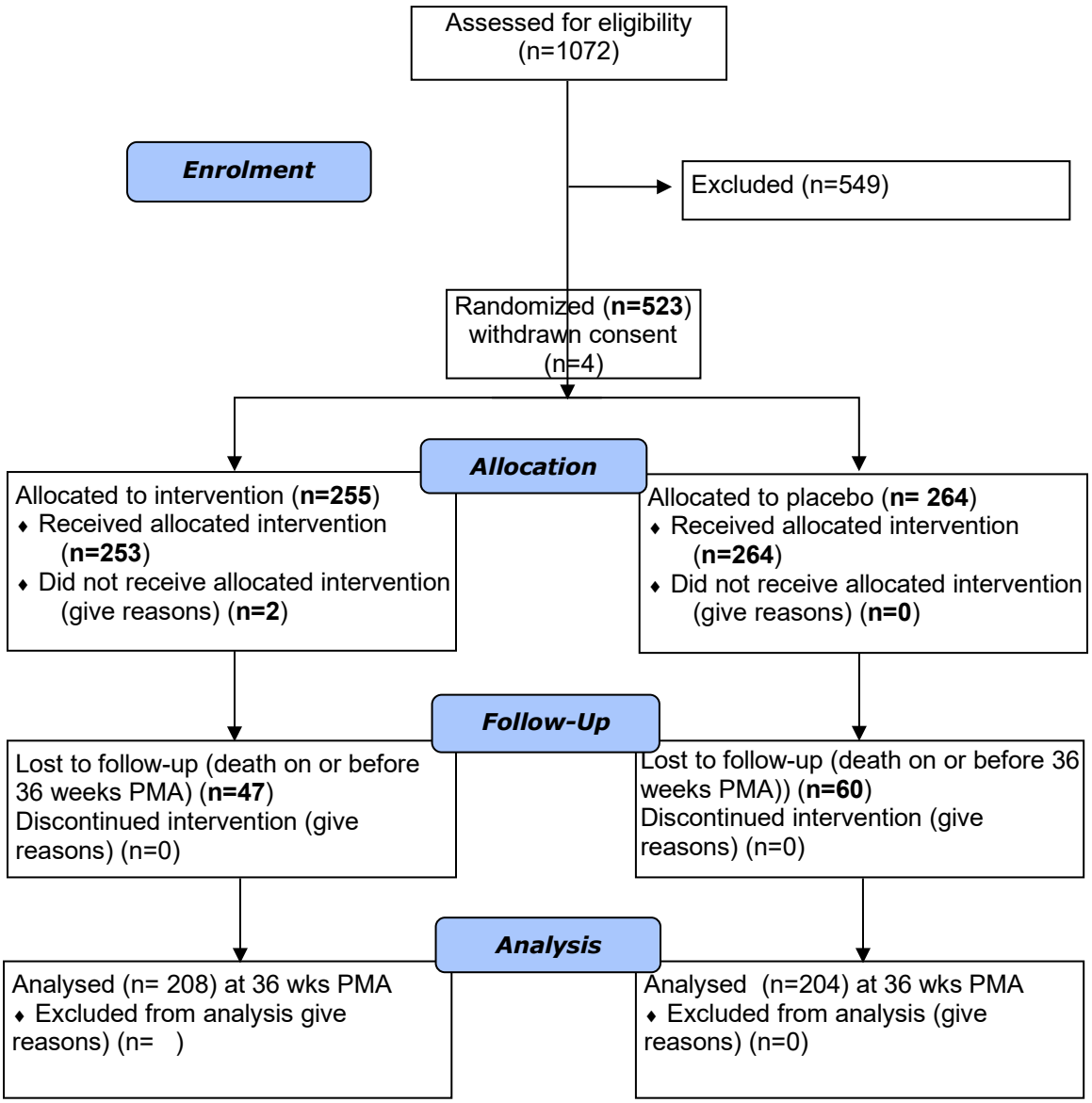
Follow-up Set (FUS): All subjects of the FAS who participated in the 2-year follow-up visit.

Modified Full Analysis Set (mFAS): As 2 subjects included in the FAS population did not receive any trial medication administration, a modified FAS was created post-hoc

Baseline data are shown for both the FAS and the FUS. The analysis of efficacy data at W36 was performed on the FAS. Sensibility analysis was performed on the mFAS. The analysis of adverse events was performed both on the SAF and the FUS. The analysis of other safety and tolerability data recorded at the year 2 visit data was performed on the FUS while the analyses of the other safety data were performed only on the SAF.

Results

Participant flow



A high number of infants n=549 were excluded from the study after the first assessment of eligibility.

The 2-year visit was performed for 197 HC subjects and 188 placebo subjects.

Recruitment

Out of the 1072 subjects screened for eligibility, 523 infants were randomised (see figure above).

The first patient was enlisted 25-May-2008, the last patients was enlisted on 12-April-2016.

Conduct of the study

The study was a French, multicentre, prospective, randomised, double-blind, placebo controlled clinical study.

The number of subjects included was lower than the calculated sample size. The study was conducted under a group sequential design, involving an interim analysis at every 100 treated subjects. At the fourth interim analysis (March 2013), the steering committee decided to stop the trial owing to financial and technical support limitations thus the analysis of the primary endpoint was performed on a limited sample size. There are concerns regarding loss of type I error control in relation to the premature study termination. In addition, remaining uncertainties exist as to whether the type I error was adjusted in the final analysis of the primary endpoint considering that this analysis was preceded by four interim analyses (OC).

A significant difference was observed between the Investigational Medicinal Product (IMP) and control groups on the main endpoint based on 521 infants (initial analysis), although the planned sample size was requiring 786 subjects. The used inferential tool was an unadjusted $\chi 2$ test of comparison of two proportions between two independent samples. This double limitation (reduced sample size and unadjusted Inferential test) has underpowered the trial. An appropriate adjustment for baseline conditions is expected to substantially improve the power of the test and the precision of the estimates. This re-analysis aims at providing results in reducing the overall residual variability of the endpoints attributable to baseline available covariates known to considerably impact the studied endpoints.

Several post-hoc analyses were performed in addition to the initial analysis.

According to the CSR, a total of 12 changes were made to the protocol. These have only been described very briefly. In addition, there are only few details provided in the protocol and protocol amendments appendix. Upon CHMP's request, the Applicant has provided all the versions of protocol in French (i.e. 6 versions). The final approved version, ie V7.0 was already submitted in both French and English in the registration dossier. These changes do not raise further concerns.

Baseline data

The mean birth weight was 867 ± 151g [median= 860g, min=597g, max=1338g] in the group receiving HCHS and 847 ± 161g [median= 860g, min=550g, max=1345g] in the placebo group.

The mean gestational age was 26.4 ± 0.9 weeks (postmenstrual age) [median = 26.4, min=23.9, max= 27.9] in the HCHS group and 26.3 ± 0.9 weeks [median = 26.5, min=23.9, max= 27.9] in the placebo group.

Antenatal corticosteroids were used for 93.3% of HCHS subjects vs 92.8% of placebo subjects. Open label glucocorticosteroid was used for 102/253 (40.3%) HCHS subjects and 108/264 (40.9%) placebo subjects. The median time between onset of study treatment and initiation of corticosteroids was 21 days in both groups, and the median duration of treatment with corticosteroids was 15 days in the HCHS group and 19 days in the placebo group.

At study entry, the majority of subjects were ventilated (204/255, 80% in the HCHS group and 217/264, 82.2% in the placebo group).

Numbers analysed

Table 5: Population of subjects

Analysis Set	HCHS	Placebo	All Subjects
Full Analysis Set (FAS)	255	264	519
Modified Full Analysis Set (mFAS)	253	264	517
Safety Set (SAF)	253	264	517
Subjects Alive at 36 weeks of PMA	208	204	412
Subjects Alive at Year 2	207	197	404
Follow-up Set (FUS)	197	188	385
Subjects with Neurological Evaluation at Year 2	194	184	378
Subjects for whom the revised Brunet Lezine test was performed	158	145	303
Subjects with Global Neurological Assessment	36	39	75

Outcomes and estimation

A total of 519 subjects (255 in the HC group and 264 in the placebo group) were randomised in the PREMILOCstudy, which is lower than the initially planned number of 786 (393 per group).

HC was administered intravenously at 0.5 mg/kg every 12 hours for 7 days, then 0.5 mg/kg every 24 hours for 3 days to premature neonates with gestational age between 24+0 and 27+6 weeks of gestation.

The primary endpoint, alive without BPD at 36 weeks of PMA, was reached significantly (p=0.04) more often in the HC group (153/255; 60.0%) vs the placebo group (135/264; 51.1%). Sixty percent of the participants in the group which received HC were alive without BDP at 36 weeks of PMA compared to 51.1% on placebo.

Neonatal all-cause mortality at 28 days was analysed post-hoc as a secondary endpoint and was seemingly similar between the two groups (84.7% and 83.7% in the HC and placebo groups, respectively). At year 2, the survival rate was numerically higher (81.2%) in the HC group than in the placebo group (74.6%). The rate of subjects receiving invasive mechanical ventilation was also investigated. It was 72.2% in the test group and 73.9% in the placebo group at baseline, decreasing to 30.7% in the test group and 41.8% in the placebo group at Day 10, i.e. a numerical difference of the same magnitude as the BPD free survival at week 36. PDA ligation was needed in 15% of the subjects in the test group and 21% in the control group.

In addition, another of the secondary endpoints is extubation rate at Day 10. At this day, 63.9 % were extubated in the test group and only 48 % in the placebo group. The difference was built up over time, starting from day 5 which appears early considering the anticipated lag time between treatment initiation and extubation. First, there is a delay between start of treatment before any pharmacological effect on lung function would be measurable and second, there is further delay before the response would lead to a decision on extubation followed by implementation. Therefore, it is questionable whether the difference recorded can be attributed to treatment. The applicant suggests that early extubation would be due to a rapid effect on lung inflammation reducing the need for reintubation. There is nevertheless no data presented supporting this assumption. Thus, the data on extubation rate, although apparently convincing, leaves remaining uncertainties limiting its value.

Summary of main efficacy results

The following tables summarise the efficacy results supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 6: Summary of Efficacy and Safety for trial PREMILOC

Title: Early Low-Dose Hydrocortisone to Improve Survival without Bronchopulmonary Dysplasia in Extremely Preterm Infants: a Randomised, Double-Blind, Placebo-controlled, Multicenter Trial			
Study identifier	PREMILOCEudraCT Number – 2007 – 002041 – 20		
Design	Phase III, multicentre, randomised, double-blind, placebo controlled clinical trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	10 days duration of treatment not applicable Follow – up – 2 years	
Hypothesis	Superiority		
Treatments groups	Neonates receiving hydrocortisone (HC)		255 neonates randomised in the HC group, 253 received at least dose of HC.
	Neonates receiving placebo		264 neonates received placebo.
Endpoints and definitions	Primary	Reduction in neonatal mortality and occurrence of BPD	Any surviving preterm infant without bronchopulmonary dysplasia at 36 weeks of amenorrhoea.
	Secondary	Impact of hydrocorti-sone on neonatal mortality and respiratory morbidities	Evaluation of impact hydrocortisone on neonatal mortality and respiratory morbidities: • Neonatal all-cause mortality at 28 days • Survival rate at 2 years of age • The rate of subjects receiving invasive mechanical ventilation • Need for PDA ligation • Use of systemic postnatal corticosteroids (hydrocortisone hemisuccinate or other steroids) beyond the treatment period by HCHS expressed as cumulative or equivalent (doses not available in the database) • Extubation rate at day 10 of life
Database lock	Not provided		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat analysis		
Descriptive statistics and estimate variability	Treatment group	HC	Placebo
	Number of subject	255	264

	Alive without BDP at 36 weeks of PMA	153/255 (60%)	135/264 (51.1%)
	significance	Reached more often vs placebo at level p=0.04	
Effect estimate per comparison	Secondary endpoint	Comparison groups	HC vs placebo
	Survival	Hazard ratio	0.75 [95%CI: 0.52;1.09]
		Day 21	87.1% vs 83.7%
		Day 28	84.7% vs 83.7%
		Year 2	81.2% vs 74.6%
	Requiring intubation day	Comparison groups	HCHS vs placebo
		Day 10	63.9% vs 48.1%
	36 weeks PMS	Comparison groups	HCHS vs placebo
		Alive	81.5% vs 77.3%
		Spontaneously air breathing	66.8% vs 58.3%
		Ventilation definitely weaned	24.4± 29.0 days of age (n=203)vs 25.1± 25.3 days of age (n=199)
		Oxygen support definitely waned	62.0±26.5 days of age (n=187) vs 66.6±30.3 days of age (n=181)
		Use of central catheter definitely discontinued	41.1±25.8 days of age (n=203) vs 43.8±30.2 days of age (n=198)
	Discharge from hospital	Mean age	102.2±54.1 days vs 98.4±40.6 days
		Alive	96.3% (207/215) vs 93.0% (200/213)
	2 years chronological age (median corrected age of 22 months)	Alive	81.2% (207/255) vs 74.6% (197/264
		BDP diagnosed at 36 weeks of PMA	26.4% (145/297) vs 33.5% (125/188)
		Additional medication received for respiratory problem	46.2% (85/184) vs 48.6% (88/181)
	Patent ductus arteriosus	Presence	51.4% (130/253) vs 60.2% (159/264)
		Need of surgical repair	14.6% (37/253) vs 21.2. (56/264)
		Hazard ratio	HR=0.63 [95%CI: 0.42-0.97], p=0.03
Notes	The trial was terminated prematurely yielding data from a smaller sample size than expected (523 were randomly assigned to treatment or placebo groups, 256 HCHS, 267 placebo), 521 subjects were included in the initial analyses (255 HCHS, 266 placebo, 2 consent withdrawals), and 519 in the present report (255 HCHS, 264 placebo, 2 delayed additional consent withdrawals).		
Analysis description	**Primary efficacy criteria:** The primary endpoint – alive without BDP at 36 weeks of PMA was reached significantly (p=0.04) more often in the HC group (153/255; 60%) placebo group (135/264, 51.1%) when analysed with the chi^2 test. This difference was confirmed using GLMM adjusting for treatment (OR: 1.54 [1.04; 2.27], p=0.03).		

3.3.6.3. Supportive information from other publications

Follow-up publications utilising PREMILOC data

Heneau 2018: The publication analysed the effects of prophylactic treatment with HC in relationship to the placental findings. Placental inflammation was associated with a significant, increased rate of BPD-free survival at 36 weeks' postmenstrual age, independent of gestational age, treatment group, and sex (adjusted odds ratio: 1.72, 95% confidence interval [CI]: 1.05 to 2.82, p = 0.03). Regarding the response to treatment, the strongest benefit of HC compared with placebo was found in infants born after placental vascular disease, with significantly more patients extubated at day 10 (risk difference: 0.32, 95% CI: 0.08 to 0.56, p= 0.004) and similar positive direction on survival without BPD (risk difference: 0.23, 95% CI: 0.00 to 0.46, p= 0.06).

Baud 2024: a post – hoc analysis assessing the efficacy outcome of the PREMILOC study taking into account the baseline risks of BPD or death was published. The treatment effect was evaluated on the primary endpoint through a covariance Analysis ANCOVA, adjusting for the baseline covariates using a mixed linear model. The interaction between treatment group and baseline risk for BPD or death was not statistically significant (p = 0.498). After adjusting for the patient's probability of BPD-free survival using baseline predictors alone, i.e. gestational age at birth, birth weight, respiratory support at baseline (RSB), sex, centre effect, and multiple pregnancy status., the HC treatment exhibited a highly significant effect (OR [95% CI] = 2.053 [1.602–2.501], p = 0.002), with a number needed to treat NNT [95% CI] = 5.8 [4.1–23.0]. Despite a weak interaction with sex, the authors found a lack of heterogeneity in the treatment effect across specific subpopulations.

Additional clinical studies with initiation of HC < 7 days of life

Besides PREMILOC, four prospective randomised, double-blind placebo-controlled studies investigating the efficacy and safety of administration of HC in premature infants were identified by the applicant.

Watterberg (2004) and Peltioniemi (2005) concluded that the early administration of HC in premature children was associated with a higher rate of survival without BPD (need for supplemental oxygen, or chronic lung disease). There were no differences vs the placebo in 2 studies that were early terminated.

Three other retrospective studies also assessed the efficacy of prophylactic HC. The 2 first ones failed to demonstrate any difference in efficacy between the periods where premature infants did not receive systematic HC and the periods where they did receive it, while there was a significant difference in the 3rd one (studies are summarised in the Table below).

Table 7: Published studies of HC in premature children. Initiation of treatment < 7 days of life

Reference	Methods	Inclusion criteria	N	HC treatment		Primary outcome	Efficacy results
				Dose	Date start		
Randomised, placebo controlled studies							
Bonsante 2007	Prospective, randomized, double- blind, placebo-controlled trial.	24-30 W of GA Birth weight: 500-1249g Need for mechanical ventilation	50 (2x25)	1 mg/kg/day for 9 days followed by 0.5mg/kg/day for 3 days	<48 h of life	Survival without need of supplemental oxygen at 36 weeks of PCA	O_2-free survival higher in HC group: 64% (16/25) vs 32% (8/25) (p=0.02)

Peltoniemi 2005	Prospective, comparative, randomized, double- blind, placebo-controlled study	≤ 30 WA, body weight from 500 to 1250g and respiratory failure	51 (HC:25, PI:26)	2.0mg/kg/day for 2 days, then 1.5mg/kg/day for 2 days, then 0.75 mg/kg/day for 6 days	<36 h of age	Survival without BDP	64% (HC) vs 54% (placebo), NS but enrol-lment of only 16% planned sample size Lower rate of patent ductus arteriosus in the HC group (36% vs 73%, p = 0.01)
Watterberg 1999	Prospective, randomised, placebo-controlled, double blind study	500-999g Mechanical ventilation	40 (2x20)	1 mg/kg/day for 9 days followed by 0.5 mg/kg/day for 3 days	<48 h of life	Survival without CLD=O_2 dependence at 36 W PCS	Better success with HC: 60% (12/20) vs 35% (7/20), p=0.02
Watterberg 2004	Prospective, randomised, placebo controlled, masked study	500-999g Mechanical ventilation	360 (2x180)	1 mg/kg/day for 12 days followed by 0.5 mg/kg/day for 3 days	12-48h of life	Survival without BPD	No difference HC: 35% (63/179); Placebo: 34% (60/178)
Retrospective studies							
Briscoe 2022	Retro-spective study before and after HC imple-mentation	< 28 weeks gestation	191 (Pre-HC:88 HC: 103)	0.5 mg/kg every 12 h for the first 7 days, followed by 0.5 mg/ kg once daily for 3 days	<24h	Safety	No difference in BPD-free survival HC: 26.2% (27/103) No HC: 27.2 (24/88) p=0.87
De Souza 2024	Retrospective study before and after HC imple-mentation	< 28 weeks gestation	147 1st group: without HC: 76, 2nd group: 71: 63 HC + 8 with no HC	NA	<24h	Survival without moderate or severe BPD	No difference Group 1 (mainly HC): 63.4% (45/71) Group 2: 52.1% (38/73)
Shah 2024	Retro-spective study comparing	<28 weeks gestation	287 (HC: 82,	0.5 mg/kg every 12 h for the first 7 days,	<24h	Survival without BPD	HC: 43.9% No HC: 40.5%

	HC- treated and not treated patients		no HC: 205)	followed by 0.5 mg/ kg once daily for 3 days			Adjusted OR: 2.04 (1.1 - 3.7), p=0.02
BPD= bronchopulmonary dysplasia; CLD= chronic lung disease GA= gestational age; PCA = postconceptional age; W= weeks							

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant referred to six reviews and meta – analyses that assessed the efficacy of early HC for the prevention of BDP (Morris 2019; Shaffer 2019; Doyle 2021; Zhou 2021; Ramaswamy 2021; Abiramalatha 2022).

Most of them concluded that the early administration of HC in premature infants was associated with an increased chance of survival without BPD (Morris 2019; Shaffer 2019; Doyle 2021; Ramaswamy 2021; Abiramalatha 2022).

In the analysis presented by Zhou et al (2021) a conclusion was made that there was prevention of combined death or BPD in infants < 1000g with chorioamnionitis exposure but not in infants without chorioamnionitis exposure.

Hay (2023) presented the network meta-analysis that compared the different corticosteroid protocols and placebo mainly concluded to the superiority of moderate dose DX for death and combined death or BPD at 36 weeks in case of early treatment initiation (see table below).

Table 8: Efficacy in reviews and meta-analyses – HC commenced within 7 days of life

Reference	Methods	Drugs	Studies included for HC	Efficacy results
Morris 2019	Systemic review and meta – analysis using methods from the Cochrane collection	HC	BPD studies (early): Baud 2016 Peltoniemi 2005; Watterberg 1999; Watterberg 2004; Bonsane	Early systemic HC significantly increased the chances of survival without BPD (RR 1.13, 95% CI [1.01, 1.26], NNT 18), (10 studies) RR 1.19 (1.04 to 1.35) for 5 BPD studies HC significantly reduced risk for treatment of PDA (all-studies: 0.66 [0.52, 0.84], p < 0.01, NNT 11
Shaffer 2019	Individual patient data meta - analysis	Low dose HC	Watterberg 2004; Peltoniemi 2005; Bonsante 2007; Baud 2016 N=982	Survival without BPD at 36 weeks PMA: significant increase with HC vs placebo: OR, 1.45; 95% CI, 1.11-1.90; p = 0.007
Doyle 2021	Cochrane review	HC DX	12 studies: Baden 1972; Batton 2012;	HC alone reduces mortality (RR 0.80, 95% CI 0.65 to 0.99; 11

			Baud 2016; Biswas 2003; Bonsante 2007; Efird 2005; Hochwald 2014; Ng 2006; Peltoniemi 2005; Watterberg 1999; Watterberg 2004 5 BPD studies	studies, 1433 infants; high-certainty evidence). BPD at 36 weeks' postmenstrual age (PMA): HC has little to no effect (RR 0.92, 95% CI 0.81 to 1.06; 9 studies, 1376 infants; high-certainty evidence). Combined outcome of mortality or BPD at 36 weeks' PMA Reduction with HC (RR 0.90, 95% CI 0.82 to 0.99; 9 studies, 1376 infants; high-certainty evidence)
Zhou 2021	Meta-analysis of 3 randomized studies	HC	Heneau 2018 (PREMILOC); Watterberg 2004; Watterberg 1999	Prevention of Combined death or BPD in infants < 1000g with chorioamnionitis exposure but not in infants without chorioamnionitis exposure
Ramaswamy 2021	Systemic review and network meta-analysis	CS	62 studies (5559 neonates) Early HC: Watterberg 1999; Efird 2005; Watterber 2004; Peltoniemi 2005; Bonsante 2007; Ng 2006; Hochwald 2014; Baud 2016	Early HC associated with decreased risk of BPD or mortality risk ratio [RR], 0.82; 95%credible interval [CrI], 0.68-0.97
Abiramalatha 2022	Umbrella review of proposed interventions for prevention of BPD	Multiple interventions	HC: Doyle 2017 – early, Doyle 2017 – late, Zhou 2021, Shaffer 2019	Early hydrocortisone prophylaxis in high-risk neonates may decrease combined risk of BPD and death at 36 weeks PMA
Hay 2013	Cochrane review; Network meta – analysis; Prevention of BDP	Systemic corticosteroids	Baden 1972; Batton 2012; Baud 2016; Biswas 2003; Bonsante 2007; Efird 2005; Hochwald 2014; Ng 2006; Onland 2019; Parikh	Early treatment (<7 days): only moderate-dose DX to decrease risk of BPD at 36 weeks PMA (RR 0.56, 95% CI 0.39 to 0.80; I2 =41.40%, 95%

			2013; Peltoniemi 2005; Watterberg 1999; Watterberg 2004	CI 3.70% to 64.40%; moderate certainty evidence* HC found preferable treatment for the prevention of mortality (P-score 0.8999). Only moderate-dose DX decreased the composite outcome of death or BPD at 36 weeks' PMA compared with control (RR 0.77, 95% CI 0.60 to 0.98; moderate-certainty evidence).
BPD: bronchopulmonary dysplasia; CI: confidence interval; DX: dexamethasone; HC: hydrocortisone; OR: odds ratio; PMA: postmenstrual age; RR: risk ratio				

Review of clinical studies with initiation of HC at any time

De Luca 2024: The aim of this systematic review and meta-analysis was to clarify if systemic HC, in protocols allowing to start it before the 15th day of life, prevents BPD or other adverse outcomes in very preterm neonates, and to identify any possible effect size modifiers. Seven trials were included (Bonsante 2007; Onland 2019; Baud 2016; Watterberg 2022; Peltoniemi 2005; Watterberg 2004; Watterberg 1999) and accounted for a total of 2193 infants. HC treatment did not reduce BPD (risk ratio (RR) 0.84 (95% CI 0.64 to 1.04)), but heterogeneity was evident (I2=51.6%). The effect size for BPD is greatest for 10–12 days duration of treatment (β=0.032 (0.01), p=0.007) and tended to be greater in patients with chorioamnionitis (β=−1.5 (0.841), p=0.07). HC treatment may significantly reduce mortality (RR 0.75 (95% CI 0.59 to 0.91)), there is no heterogeneity (I2=0) and the reduction tended to be greater in males (β=−0.06 (0.03), p=0.07). HC may significantly reduce necrotising enterocolitis (NEC; RR 0.72 (95% CI 0.53 to 0.92)); there is neither heterogeneity (I2=0%) nor any effect size modifiers. HC did not affect other adverse outcomes of prematurity. De Luca et al concluded that HC may be considered, on a case-by-case evaluation, to reduce mortality and NEC, while it does not affect BPD; and that there are some potential effect size modifiers for mortality and BPD which should be addressed in future explanatory trials.

3.3.7. Discussion on clinical efficacy

Design and conduct of the clinical studies

Introduction

This application is based on a hypothesis which has been discussed since the 1990:s, i.e. that low cortisol concentrations and an immature hypothalamic–pituitary–adrenal axis in the first postnatal weeks hinders normal adaptation to the intense stress associated with preterm conditions. This inability to adequate response has been linked to pulmonary inflammation and the development of BPD. Substitution with low dose HC during the first days of life has therefore been suggested to prevent BPD in premature infants born before 28 weeks of gestation.

Since the 1990:s a number of smaller studies have been conducted and in 2016, there was a publication in the Lancet from a larger study conducted to confirm the above hypothesis. This study (PREMILOC) is pivotal in this MAA. The database behind PREMILOC was first presented in 2016, i.e. a number of years before the data were summarised to substantiate the current application. Following this first publication (which includes the data presented as pivotal below), two *post-hoc* analyses (Baud 2024 and Héneau 2018) were published. Baud 2024 investigated the data corrected for certain background factors whereas Héneau 2018 discussed effects of placental inflammation. The PREMILOC database was also used for a prespecified secondary analysis (Renolleau 2021) where the association between baseline cortisol and the effect of prophylactic HC was investigated. In addition, neurodevelopmental outcomes at 2 years of age were presented in separate publications. In the assessment of this application, the focus is on the primary/final analysis. The various *post-hoc* and secondary analyses of the data are not considered to be key.

Dose finding

Different doses and treatment durations are described in the literature, including higher doses leading to negative effects (see the clinical safety part). The dose applied in PREMILOC (i.e. 0.5 mg/kg BID for 7 days followed by SID for 3 days, starting at the day of birth) was chosen to be at the lower end of the dose range suggested at the time. There are no dedicated dose finding studies conducted, which is accepted. Indeed, considering the vulnerable target population and the special situation when treatment is initiated, it would not be realistic to include several dose groups in a clinical trial. The absence of dose determination is thus justified. Notably, the dose level suggested is generally in line with products approved for replacement therapy of adrenal insufficiency in infants.

Study design

PREMILOC is a multicentre, randomised, double blind, placebo-controlled study. It was conducted in France between 2008 and2016 in two phases with BPD free survival at 36 weeks of age as the first objective and neurodevelopment at 2 years as the second. The presentation of the study conduct is complex as the study was finalised and the results published - including a number of follow-up analyses, before the data were summarised in the format intended for submission of the present application.

Study population

Newborns with a gestational age between 24^{+0} and 27^{+6} weeks were included. Nevertheless, no corresponding restriction appears in the proposed indication as expressed in the SmPC Section 4.1. Upon request, the applicant agreed to restrict the indication accordingly.

A total of 523 subjects were randomised. The inclusion and exclusion criteria were appropriate to identify the target population at the time. As the study was conducted in 2008-2016 (including the two-year follow up) at multiple centres in France, there is a delay of more than 10 years from the evaluation of the primary endpoint to the submission of the MAA and the database covers the treatment practice in one single country only. Since PREMILOC was conducted, standard of care (SOC) has developed with the aim to decrease the risk for BPD. There has been continuing efforts to minimise barotrauma from ventilatory support and consequently reduce the risk for BPD. SOC also varies between centres, regions, and countries making extrapolation between populations difficult. It is therefore uncertain to what extent the results from the results obtained from PREMILOC could be replicated in a modern setting**.** In the PREMILOC study, premature infants with a birth weight of <500 grams or a birth weight below the 3rd percentile for gestational age were excluded.

Endpoints

The primary endpoint of the study was BPD free survival at week 36. The definition of BPD is as according to the standard applied at the time the study was conducted. It is stated as need for ventilatory support using either mechanical or continuous positive airway pressure (CPAP) ventilation, or spontaneous ventilation with the need for FiO 2 ≥ 30%, or spontaneous ventilation with FiO 2 < 30% but a failure in oxygen reduction test (Walsh test) showing true oxygen dependency. The timepoint 36 weeks is standard when assessing BPD.

As a long-term primary endpoint, neurocognitive development at 18-24 months of corrected age is listed, using a revised Brunet-Lézine (RBL) scale. These data are presented in the safety part.

There were no secondary endpoints included in the original SAP. Results from a number of secondary endpoints were nevertheless reported *post-hoc* (see results below).

Statistical analysis plan

The PREMILOC study was not planned to meet regulatory requirements or to be used in the current context. This has been made very clear by the applicant and is stated to be one reason why there exists a second version of the SAP in addition to the original SAP. Another reason is the fact that upon acquisition of the rights to the database, the applicant received the database with two missing subjects due to two withdrawals of consent from data disclosure. The second version of the SAP ("PIP Additional SAP") describing the re-analysis of study data was written after all trial data was collected, and with the authors having access to the complete locked database. According to the applicant, the database was officially locked February 4, 2017. The database was transferred to the applicant in early 2018. The PIP Additional SAP version 3.0 is dated 22 February 2024. According to this, version 1.0 was dated 24 June 2019.

An "Operational SAP" (version 2.0 dated 12 December 2023) was also submitted. The applicant has stated that this SAP was prepared for practical reasons. In addition, there exists a separate report titled "Hydrocortisone to prevent Broncho-Dysplasia in Neonates Supplemental Analysis" (version 1.0 dated 31-01-2024).

The applicant appears transparent in the case additional or *post-hoc* analyses have been performed. However, although the original SAPs and statistical reports have been submitted, it required some effort to try to penetrate what had been originally planned in comparison with the second version/additional SAP authored by the applicant.

Interim analyses

The PREMILOC study was planned to use a randomised triangular test (Whitehead et Stratton, 1983) allowing for sequential testing of the primary endpoint success rate. An interim analysis was to be performed each time a group of 100 consecutive preterm infants had been assessed.

After the fourth interim analysis (March 2013), the PREMILOC steering committee decided to stop the trial owing to financial and technical support limitations.

To ensure strict control of the type I error rate and to avoid concerns regarding study integrity, the decision to stop the study should have been based on one of the pre-specified criteria (efficacy, futility, safety). In the SAP authored by the applicant, it was stated that "despite the premature termination of the trial, a significant difference was observed among the trial endpoints, accounting for the correction of the type I error due to the unfinished future planned analyses". Details were lacking, and the applicant was requested to clarify whether and if so, how, the interim analysis plan allowed that the final analysis could be performed earlier and despite that none of the pre-defined criteria had been met. Details were also requested regarding what went on between interim analysis four and the date for the last subject last visit for the week 36 PMA analysis.

In their response the applicant explained that after it had been decided to terminate the study early, the stop date was set with the objective to reach 500 neonates such that a 5th interim analysis could be performed to serve as the final analysis of the primary endpoint. The preplanned sequential test procedure based on a triangular test was then modified by the use of an adapted truncated triangular test which will have implied that updated boundaries could be derived.

To support the claim that the final analysis of the primary endpoint can be considered type I error protected the applicant also submitted a re-analysis of the original sequential test design and a re-calculation of the boundaries for the fifth and final analysis. The applicant clarified that the triangular test is not based on an alpha spending error, but on an overall preservation of the type-1 error over the whole inspection of the group sequential test and hence that the used design is characterised by an overall type-1 error bounded by $\alpha=0.025$ at the 5th and last inspection.

Nevertheless, the early stop of the study will have necessitated an appropriate adapted truncated triangular test design. The adapted version will have been determined as the same original 1-sided triangular test, and the same boundaries for the four first analyses, but was followed by a truncation at a pre-determined point of 500 infants corresponding to the maximum possible sample size for a last 5th inspection. A critical value had to be determined to ensure the predetermined overall significance level ($\alpha\leq0.25$). The applicant has stated that the calculation of the critical value was performed by a third-party statistician that was blind at any time to the trial data. This critical value will have been locked before the last/final analysis.

The truncated triangle test will have been fully determined and locked on 5 September 2014. This is supported insofar that the history of modifications included in the original statistical analysis report on the same date confirms "Addition of triangular test".

According to the applicant's response, the fifth analysis will have been performed on 12 September 2014. This seems not to be confirmed by the original statistical analysis report.

The truncated triangular test was mentioned under the heading "Specific statistical methods" already in the original SAP document dated as of 8 January 2014 (i.e. before the study was stopped), including a calculation of the critical value based on a final sample size of 521 neonates as well as the value observed. According to this SAP, the critical value was 10.400435 and the observed value was 10.87064.

According to the applicant's response, the original adapted truncated test will have implied a decision rule of accepting H0 if the observed last Z value was <11.4138, otherwise H0 was to be rejected. When the 5th interim analysis was performed (12/09/2014), the observed Z5 will have been 11.5508.

Contributing to a slight confusion regarding the order of events and concerns regarding study data integrity, is the statement in the original statistical analysis report dated 10 June 2014 declaring "Final analysis of all the patients. The interim analysis was stopped at 4 analyses".

All considered, the CHMP is still not fully convinced that the type I error control was maintained in the final analysis of the primary endpoint. There is still a potential concern regarding the order of events pertaining to what appears to have been the performing of the final analysis based on the final number of randomised subjects ahead of the derivation of adapted boundaries by a third party and the potential impact on study data integrity as well as a potential concern regarding why, as it seems, a fifth interim analysis as initially planned based on N=500 was not performed before a final analysis including potential over-running subjects. Thus, the applicant is requested to perform the statistical test of the primary endpoint based on the initial plan, i.e. the original triangular test performed as planned at the fifth IA with N=500.

According to the PREMILOC study protocol, the steering committee was to be composed of the physicians initiating the project, the biostatistician in charge of the project, representatives of the sponsor and of the CRU appointed for this research. A critical issue is whether the steering committee had any knowledge of IA results when the decision was made to stop the study. The applicant is requested to explain and provide what evidence there might be, e.g. steering committee meeting minutes and independent monitoring committee meeting minutes.

The original SAP did not include any multiple testing procedure to assure type I error control for the analysis of secondary endpoints. Thus, even if the primary endpoint conclusion nonetheless would pertain to a true rejection of the null hypothesis, a major concern still is that it is questionable whether the result from the primary endpoint is sufficiently compelling by itself to confirm that a clinically meaningful effect has been established.

Original and repeated statistical analysis

The applicant has explained that no analysis populations were defined in the original SAP. This is acknowledged. However, initially, it had been defined that the original analysis was to be performed according to the principle of ITT. The primary efficacy analysis approach, whether in original, or, as performed by the applicant, implied analyses based on all randomised subjects (i.e., FAS). This is endorsed. As primary evidence, it is paramount that the applicant has repeated the primary analysis of the primary endpoint as originally planned. This analysis was based on an unadjusted chi-2 test. The applicant has stated that there were no specific secondary analyses described in the original SAP. This is acknowledged. The lack of pre-specified analysis methods in combination with the lack of a multiple testing procedure in the original SAP results in a cautious approach in interpreting any secondary efficacy endpoint outcomes.

Post-hoc analyses

A modified FAS was created *post-hoc* (defined in the operational SAP). It was used for a sensitivity analysis of the primary endpoint excluding 2 subjects from the HC arm who did not receive any randomised treatment. This analysis is not deemed as useful.

Further, the applicant has performed adjusted analyses of the primary endpoint.

Given that randomisation was stratified, the analysis of the primary endpoint adjusted for the stratification variables is considered to be of interest. Taking centre into account may be relevant since, according to the clinical study protocol, a multicentre study was considered "necessary in order to recruit a sufficient number of patients and to take into consideration the difference in severely preterm infant management between level III perinatal centres" (see below, Efficacy data and additional analyses).

Since the PREMLOC study was stopped before the planned number of preterm infants (786) had been randomised, the applicant stated that a modification to the main model was required to maintain the power. However, once a trial is completed, the results generally supersede any calculations of power carried out before the trial was undertaken. This exercise aimed at decreasing variability and producing a *post-hoc* analysis of the primary endpoint adjusted for several baseline covariates (claimed to be of importance). The initial conclusion was that this analysis cannot be accepted as part of the primary evidence.

In response to a concern relating to that the precision of the primary effect estimate leaves a substantial risk for random error, the applicant referred to the same exercise. Although seemingly thorough this was *post-hoc*. Since there may be a number of alternative valid analyses, results based on pre-specified analyses carry most credibility. The initial conclusion has not changed.

The result from this predictive model development was an analysis model including gestational age, weight at baseline, sex, need for respiratory support at baseline and multiple pregnancy. Compared with the control group, the observed treatment effect in this *post-hoc* analysis adjusted for the other covariates was 1.82 (95% CI [1.16; 2.85], p=0.009]. In this respect, besides the predefined primary analysis (based on the unadjusted chi-2 test, crude OR: 1.48, p=0.04), the only other analysis that is considered sufficiently stringent to serve as support for the effect size is the analysis adjusted for both the stratification variables (see below).

Based on the decision to stop the study, the number actually randomised was 523 (256 HCHS, 267 placebo). The original initial report included an efficacy analysis of data from 521 subjects as parents withdrew their consent for 2 subjects, one subject from each arm. Due to two additional withdrawals of consent from data disclosure upon acquisition of the rights to the database, the applicant received the database with two more missing subjects, both randomised to placebo. Thus, the analysis presented by the applicant is based on 519 subjects in total.

Efficacy data and additional analyses

Participant flow

Of the 255 subjects in the HC group and 264 in the placebo group, 47 and 60 respectively died before week 36. A total of 207 subjects in the HC group and 197 placebo subjects were alive at 2 years of age. Of these, 197 and 188 subjects were respectively available for the 2-year evaluation. Withdrawal from the study for other reasons than death was thus limited.

A high number of patients in the PREMILOC study received open-label glucocorticoids as concomitant medication at some point during the study. The applicant was therefore requested by the CHMP to discuss the potential impact of open-label glucocorticoid treatment between day 10- and 36-weeks PMA on the development of BPD in the trial population. The applicant stated that open-label GC exposure between day 10 and 36 weeks is unlikely to be responsible to change study outcomes regarding BPD incidence at term. This exposure was not found different between placebo and treatment group.

Baseline data

The two study groups are generally well balanced with regard to demography and different factors which may be effect modulators (such as e.g. antenatal steroid treatment which was given to most women in both groups).

Efficacy outcome

The primary endpoint, alive without BPD was achieved in 60.0% (153/255) in the HC group vs 51.1% (135/264) in the placebo group at 36 weeks MPA. The p-value for this difference was 0.042. In addition, uncertainties still exist as to whether the type I error can be considered to have been controlled given that the study was stopped prematurely without any of the predefined stopping boundaries having been met and implying that the final analysis was preceded by 4 interim analyses.

As already commented on above, the applicant is requested to provide the original triangular test performed as planned at the fifth IA with N=500. However, even if the primary endpoint conclusion nonetheless would pertain to a true rejection of the null hypothesis, a major concern still is that it is questionable whether the result from the primary endpoint is sufficiently compelling by itself to confirm that a clinically meaningful effect has been established.

In an analysis of the primary endpoint using GLMM (generalised linear mixed model) adjusting for "treatment and stratum", the outcome, comparing HC vs placebo, was an odds ratio of 1.54 [95% CI: 1.04; 2.27, p=0.03]. Whether this analysis accounted for both stratification factors (gestational age

and centre) was not clear. The applicant confirmed that the outcome of the primary endpoint as of above was based on an analysis adjusted for both gestational age and centre, i.e. the randomisation stratification variables. The GLMM always included centre as a random effect. The applicant was further requested to perform subgroup analyses based on "centre". This analysis was provided: the applicant's notation that the separate results for each centre must be interpreted with caution due to small sample sizes is agreed. The Forrest plot was nevertheless appreciated clarifying, among other things, the number of centres and the number of preterm children randomised per centre. As was clarified, one centre recruited more than 100 patients. In addition, small centres with a sample size less than 10, and two centres (12 and 19) not having randomised any subjects in either the control or the IMP arm, were excluded in the presentation of descriptive results.

Neonatal all-cause mortality at 28 days was analysed *post-hoc* as a secondary endpoint and was seemingly similar between the two groups (84.7% and 83.7% in the test and placebo groups, respectively). At year 2, the survival rate was numerically higher (81.2%) in the test group than in the placebo group (74.6%). The rate of subjects receiving invasive mechanical ventilation was also investigated. It was 72.2% in the test group and 73.9% in the placebo group at baseline, decreasing to 30.7% in the test group and 41.8% in the placebo group at Day 10, i.e. a numerical difference of the same magnitude as the BPD free survival at week 36. PDA ligation was needed in 15% of the subjects in the test group and 21% in the control group. Conclusions on statistical significance can nevertheless not be drawn for any of the secondary endpoints.

One secondary endpoint showing numerically interesting results is extubation at Day 10. At this day, 63.9% were extubated in the test group and only 48% in the placebo group, i.e. a quite prominent difference. The difference was built up over time, starting from day 5 which appears early considering the anticipated lag time between treatment initiation and extubation. First, there is a delay between start of treatment before any pharmacological effect on lung function would be measurable and second, there is further delay before the response would lead to a decision on extubation followed by implementation. Therefore, it is questionable whether the difference recorded can be attributed to treatment. The applicant suggests that early extubation would be due a rapid effect on lung inflammation reducing the need for reintubation. There is nevertheless no data presented supporting this assumption. Thus, the data on extubation rate, although apparently convincing, leaves remaining uncertainties limiting its value.

Baseline cortisol levels were discussed in the paper by Renolleau *et al* 2021. They did not find a predictive value of cortisol levels measured before 24 hours following birth for BPD-free survival. They state that increased values were associated with a higher chance of BPD-free survival in placebo-treated infants, and this association was not observed for infants treated with HC. Interpretation of this finding is nevertheless difficult.

There are no long-term data in PREMILOC supporting the efficacy of the product. Data on neurocognitive development at 18-24 months of corrected age using a revised Brunet-Lézine (RBL) scale are provided (see safety part) but without any objective of showing superiority for the test product. It would have been valuable if data on lung function at year 2 or year 5 had been available but this is not the case.

Additional data provided

In addition to PREMILOC, the applicant refers to data from four prospective randomised trials, all of them conducted before PREMILOC (Bonsante 2007, Watterberg 1999, Peltoniemi 2005 and Watterberg 2004). They all concerned early administration of HC in premature children before the 7th day of life. Three of them applied the same dose (1 mg daily) whereas the fourth applied a higher dose. Two of the studies were terminated early due to side effects attributable to NSAID. A higher rate of survival without BPD was recorded in two of the studies (Bonsante 2007 and Watterberg 1999). Watterberg

1999 was a small study which is too old to be of relevance today and Bosante 2007 is difficult to interpret as it was terminated early. Peltoniemi 2005 and Watterberg 2004 did not report any benefit from treatment, the former was terminated early. Overall, none of these four studies support benefit of treatment.

Shah 2024 was a retrospective study where efficacy parameters were investigated. Survival without BPD among extremely preterm infants who received prophylactic early low-dose HC was compared with those who did not. Firm conclusions on differences between groups cannot be drawn as the two groups were not balanced and the results indicated that treated subjects had lower gestational age at birth and were lighter. They were also deemed to be at higher risk of BPD or death according to the NICHD Neonatal Research Network 2011 BPD Outcome Estimator. Overall, these data are nevertheless of interest as they point at the profession's intention to select patients for treatment rather than treating the full population <28 weeks of gestational age.

Overall, there are several remaining uncertainties pertaining to the benefit of the product. The primary endpoint in PREMILOC was barely met and, the secondary endpoints should be interpreted with caution as they were not type I error controlled and are all based on *post-hoc* analyses. Considering the uncertainties with regard to both the effect estimate for the primary endpoint and the lack of confirmation from other data sources, efficacy is currently not deemed established. The applicant is therefore requested to discuss the benefit/risk balance and comment on whether it can at all be regarded as positive. A quite modest and statistically not compelling effect was recorded on the need for ventilatory support at 36 weeks while there are remaining concerns over study integrity and type I error control. In addition, there is no supportive information on long-term efficacy or else support from secondary endpoints. The robustness of the effect estimate in PREMILOC is thus questioned. There is also limited support from other sources available. Reviews and meta-analysis cannot be used to contextualise PREMILOC as PREMILOC data dominates the databases in these publications. Furthermore, it is uncertain to what extent the results from PREMILOC are relevant for neonatal care today as standard of care has developed over the 10 years that have passed since PREMILOC was conducted. There has been continuing efforts to minimise barotrauma from ventilatory support, and consequently reduce the risk for BPD. It is thus uncertain whether the results obtained from PREMILOC could be replicated in a modern setting.

3.3.8. Conclusion on clinical efficacy

The MAA is based on the hypothesis that low cortisol concentrations and an immature hypothalamic–pituitary–adrenal axis in the first postnatal weeks, hinders normal adaptation to the intense stress associated with preterm conditions. This hypothesis was tested in a single pivotal trial (PREMILOC) finalised in 2016 and it is uncertain to what extent the results could be extrapolated the contemporary target population. There are many uncertainties pertaining to the effect estimate, excluding firm conclusions on the primary endpoint. The secondary endpoints should also be interpreted with caution as they were not type I error controlled and are all *post-hoc* analyses. Considering the uncertainties with regard to both the effect estimate for the primary endpoint and the lack of confirmation from other data sources, efficacy is currently not deemed established.

3.3.9. Clinical safety

3.3.9.1. Safety data collection

All information required by the protocol had to be provided in the e-CRF and the investigator had to explain all missing information.

Safety parameters performed at 12 and 24 hours after treatment initiation, and every day from D2 to D10 were as follows: vital signs, ventilation parameters, concomitant treatments and adverse events (AEs).

Examinations / Date	T0	H12 after initiation of treatment	H24 after initiation of treatment	D2 - D10	D21	D28	36 wks PMA	40PMA	Visit 1 yr	Visit 2 yrs
Acceptable time		+/- 1 h		+/- 6h	+/- 1 day		+/- 3 days	+/- 1 week	+/-3 month	+/- months
Consent	X									
Clinical examination	X*				X	X	X*		X*	X*
Vital parameters	X	X	X	X	X	X	X	X		X	X
SaO_2	During the study period, at baseline and every 24 hours until the end of treatment									
Ventilation parameters (FiO_2, OI)										
O_2 dependence							X			
Radio chest	X					X				
Brain MRI								X		
Echocardiography (between D2 and D10)				X						
Cranial ultrasound	X				X		X			
Sampling for determination of total cortisol BEFORE THE 1st INJECTION	X									
Determination of T4 and TSH					X					
Creative assay protein, procalcitonin, Interleukins	X									
Blood bank, DNA library	X									
Concomitant treatments	X	X	X	X	X	Corticosteroids				
Adverse events and severe adverse events		X	X	X	X	X	X	X	Reporting of deaths and SAEs potentially related t any experimental drug	
Survival							X		X	X
Neurocognitive evaluation using the Revised Brunet Lézine scale										X*

During the on-treatment period (i.e., the first 3+7 days) AEs were, according to the flowchart, checked and documented daily in the eCRF. After this period, AEs were collected at D21, D28 and at 36 weeks PMA. After 36 weeks PMA only SAEs and deaths potentially related to the study drug was documented. Thus, AE information after 36 weeks PMA is considered incomplete.

3.3.9.2. Patient exposure

The exposure was evaluated in the safety population. Median treatment duration was 10 days and the median number of administrations was 17 in both groups (active and placebo).

A total of 165/220 (75.0% of available data) HC subjects with an available assessment and 162/232 (69.8% of available data) placebo subjects with an available assessment completed the study.

In PREMILOC, safety data up to 2 years is available in 197/253 in the HC group and 188/264 in the placebo group (i.e., the FUS population).

3.3.9.3. Adverse events

Any AE, serious or non-serious, observed up to the 36 weeks of PMA visit was to be reported. Only deaths and SAEs potentially related to experimental drug, were to be notified up to 2 years of age.

AE data were coded using MedDRA version 18.0. AE analyses and tables include all events within the treatment-emergent safety reporting period, defined as the day of the first dose of study drug through the end of the study.

Summary of treatment emergency adverse events during the whole study (SAF) is presented in table 18

Summary of Adverse Events from D1 to D10 (SAF) is presented in table xx.

Summary of Adverse Events (SAF) from D11 to 36 weeks of PMA is presented in table xy.

During both the **on-treatment (D1-D10)** as well as during the **follow up D11-36 weeks PMA** period similar or slightly lower proportions of the subjects reported any AEs, severe AEs, SAEs, any related SAEs or fatal AEs in the HCHS treatment group compared to placebo.

In both treatment groups, a higher proportion of the children with a birth age < 26 weeks PMA reported these events compared to the children with a birth age ≥26 weeks PMA. The difference between the two PMA birth ages was, in both treatment groups, especially pronounced for **fatal events** (On-treatment: HCHS < 26 w PMA 24.4% vs 4.7% for HCHS ≥ 26 weeks PMA; Off-treatment: HCHS < 26 w PMA 23.2% vs 5.8% for HCHS ≥ 26 weeks PMA). During the on-treatment period, a slight difference between the two treatment groups were noted for fatal events in the < 26 weeks PMA (HCHS < 26 weeks PMA: 24.4% vs 16.7% for placebo < 26 weeks PMA).

Table 9: Summary of treatment emergency adverse events (SAF)

	HCHS (N = 253)			Placebo (N = 264)		
	n	%	nae	n	(%)	nae
Any TEAE	227	(89.7%)	1417	253	(95.8%)	1428
Any Serious TEAE	191	(75.5%)	591	201	(76.1%)	587
Any Serious TEAE related to study treatment according to the investigator	14	(5.5%)	18	12	(4.5%)	16
Any Fatal TEAE	47	(18.6%)	103	66	(25.0%)	146
Any TEAE with onset till 36 weeks of PMA	225	(88.9%)	1347	252	(95.5%)	1384
Any TEAE with onset after 36 weeks of PMA	26	(10.3%)	70	22	(8.3%)	44

N = Number of subjects within the group, n = Number of subjects within the category, nae = Number of adverse events, TEAE = Treatment-Emergent Adverse Event, HCHS = Hydrocortisone Hemisuccinate, PMA = Post-Menstrual Age; CI = 95% Clopper-Pearson Confidence Interval, OR = Odds Ratio, RD = Risk Difference (HCHS - Placebo).

Table 10: Summary of Adverse Events from D1 to D10 (SAF)

	HCHS			Placebo		
	<26.0 Wks PMA (N = 82) n (%) nae	≥26.0 Wks PMA (N = 171) n (%) nae	All subjects (N = 253) n (%) nae	<26.0 Wks PMA (N = 90) n (% nae	≥26.0 Wks PMA (N = 174) n (%) nae	All subjects (N = 264) n (%) nae
Any AE	76 (92.7%) 313	121 (70.8%) 433	197 (77.9%) 746	85 (94.4%) 359	144 (82.8%) 461	229 (86.7%) 820
Any Severe AEs	76 (92.7%) 255	121 (70.8%) 355	197 (77.9%) 610	85 (94.4%) 298	144 (82.8%) 369	229 (86.7%) 667
Any Serious AE (SAE)	61 (74.4%) 120	86 (50.3%) 159	147 (58.1%) 279	67 (74.4%) 141	85 (48.9%) 162	152 (57.6%) 303
Any Serious AE related to study treatment according to the investigator	6 (7.3%) 8	8 (4.7%) 10	14 (5.5%) 18	3 (3.3%) 7	9 (5.2%) 9	12 (4.5%) 16
Any Fatal AE	20 (24.4%) 31	8 (4.7%) 12	28 (11.1%) 43	15 (16.7%) 29	15 (8.6%) 34	30 (11.4%) 63

N = Number of subjects within the group, n = Number of subjects within the category, nae = Number of adverse events, AE = Adverse Event, HCHS = Hydrocortisone Hemisuccinate, PMA = Post-Menstrual Age

Table 11: Summary of Adverse Events (SAF) from D11 to 36 weeks of PMA

	HCHS			Placebo		
	<26.0 Wks PMA (N = 82) n (%) nae	≥26.0 Wks PMA (N = 171) n (%) nae	All subjects (N = 253) n (%) nae	<26.0 Wks PMA (N = 90) n (% nae	≥26.0 Wks PMA (N = 174) n (%) nae	All subjects (N = 264) n (%) nae
Any AE	62 (75.6%) 236	114 (66.7%) 365	176 (69.6%) 601	71 (78.9%) 253	109 (62.6%) 311	180 (68.2%) 564
Any Severe AEs	61 (74.4%) 206	114 (66.7%) 327	175 (69.2%) 533	71 (78.9%) 223	108 (62.1%) 255	179 (67.8%) 478
Any Serious AE (SAE)	52 (63.4%) 115	69 (40.4%) 154	121 (47.8%) 269	57 (63.3%) 132	74 (42.5%) 130	131 (49.6%) 262
Any Serious AE related to study treatment according to the investigator	0 (0%) 0	0 (0%) 0	0 (0%) 0	0 (0% 0	0 (0%) 0	0 (0%) 0
Any Fatal AE	19 (23.2%) 39	10 (5.8%) 20	29 (11.5%) 59	26 (28.9%) 52	10 (5.7%) 17	36 (13.6%) 69

N = Number of subjects within the group, n = Number of subjects within the category, nae = Number of adverse events, AE = Adverse Event, HCHS = Hydrocortisone Hemisuccinate, PMA = Post-Menstrual Age

Table 12: Treatment Emergent Adverse Events by System Organ Class (SAF)

MedDRA (V18.0) System Organ Class Preferred Term	HCHS (N = 253) n (%) nae	Placebo (N = 264) n (%) nae
Any TEAE	**227 (89.7%) 1417**	**253 (95.8%) 1428**
Infections and infestations	156 (61.7%) 292	138 (52.3%) 247
Congenital, familial and genetic disorders	132 (52.2%) 216	161 (61.0%) 265
Metabolism and nutrition disorders	116 (45.8%) 247	115 (43.6%) 253
Nervous system disorders	95 (37.5%) 163	98 (37.1%) 160
Respiratory, thoracic and mediastinal disorders	79 (31.2%) 176	92 (34.8%) 181
Surgical and medical procedures	56 (22.1%) 67	79 (29.9%) 84
Vascular disorders	42 (16.6%) 60	47 (17.8%) 77
Gastrointestinal disorders	45 (17.8%) 93	33 (12.5%) 65
General disorders and administration site conditions	22 (8.7%) 25	23 (8.7%) 27
Cardiac disorders	12 (4.7%) 16	26 (9.8%) 31
Renal and urinary disorders	15 (5.9%) 15	18 (6.8%) 20
Eye disorders	14 (5.5%) 19	6 (2.3%) 8
Blood and lymphatic system disorders	7 (2.8%) 7	1 (0.4%) 1
Investigations	4 (1.6%) 12	4 (1.5%) 4

N = Number of subjects within the group, n = Number of subjects within the category, nae = Number of adverse events. TEAE = Treatment-Emergent Adverse Event, HCHS = Hydrocortisone Hemisuccinate; Ordering of MedDRA System Organ Class is based on descending frequency of subjects with events in the total population

Table 13: Most frequently reported treatment-emergent adverse events (copied from proposed SmPC section 4.8)

System organ Class/ Adverse events (in ≥ 5% of patients)	Hydrocortisone (N=253)		Placebo (N=264)	
	Any TEAEs	Serious TEAEs	Any TEAEs	Serious TEAEs
Infections and infestations	**156 (61.7%)**	**85 (33.6%)**	**138 (52.3%)**	**66 (25.0%)**
Sepsis neonatal	131 (51.8%)	-	125 (47.3%)	-
Sepsis	22 (8.7%)	22 (8.7%)	16 (6.1%)	16 (6.1%)
Septic shock	20 (7.9%)	20 (7.9%)	16 (6.1%)	15 (5.7%)
Staphylococcal sepsis	21 (8.3%)	21 (8.3%)	15 (5.7%)	14 (5.3%)
Congenital, familial and genetic disorders	**132 (52.2%)**	**11 (4.3%)**	**161 (61.0%)**	**13 (4.9%)**
Patent ductus arteriosus	130 (51.4%)	9 (3.6%)	159 (60.2%)	9 (3.4%)
Metabolism and nutrition disorders	116 (45.8%)	114 (45.1%)	115 (43.6%)	114 (43.2%)
Hyperglycaemia	113 (44.7%)	81 (32.0%)	115 (43.6%)	81 (30.7%)
Glucose tolerance impaired	16 (6.3%)	16 (6.3%)	17 (6.4%)	17 (6.4%)
Increased insulin requirement	15 (5.9%)	15 (5.9%)	18 (6.8%)	18 (6.8%)
Nervous system disorders	95 (37.5%)	47 (18.6%)	98 (37.1%)	50 (18.9%)
Intraventricular haemorrhage	90 (35.6%)	38 (15.0%)	87 (33.0%)	40 (15.2%)
Respiratory, thoracic and mediastinal disorders	**79 (31.2%)**	**72 (28.5%)**	**92 (34.8%)**	**76 (28.8%)**
Pulmonary arterial hypertension	36 (14.2%)	29 (11.5%)	44 (16.7%)	33 (12.5%)
Pulmonary haemorrhage	25 (9.9%)	20 (7.9%)	28 (10.6%)	16 (6.1%)
Respiratory depression	15 (5.9%)	15 (5.9%)	12 (4.5%)	12 (4.5%)
Hypoxia	13 (5.1%)	12 (4.7%)	14 (5.3%)	14 (5.3%)
Surgical and medical procedures	**56 (22.1%)**	**40 (15.8%)**	**79 (29.9%)**	**58 (22.0%)**
Patent ductus arteriosus repair	35 (13.8%)	35 (13.8%)	55 (20.8%)	55 (20.8%)
Inhalation therapy	24 (9.5%)	-	23 (8.7%)	-
Vascular disorders	**42 (16.6%)**	**21 (8.3%)**	**47 (17.8%)**	**31 (11.7%)**
Hypotension	38 (15.0%)	18 (7.1%)	41 (15.5%)	26 (9.8%)
Gastrointestinal disorders	**45 (17.8%)**	**31 (12.3%)**	**33 (12.5%)**	**25 (9.5%)**
Necrotising colitis	19 (7.5%)	13 (5.1%)	13 (4.9%)	11 (4.2%)

Table 14: Most common (in ⩾ 5% of patients) AEs between D1 and D10 (on treatment period) by gestational age (SAF)

System organ Class/ Adverse events (in ≥ 5% of patients)	HCHS (N=253)			Placebo (N=264)		
	Any AE			Any AE		
	<26.0 Wks PMA (N = 82) n (%) nae	>=26.0 Wks PMA (N = 171) n(%) nae	All patients (N=253) n(%) nae	<26.0 Wks PMA (N = 90) n (%) nae	>=26.0 Wks PMA (N = 174) n(%) nae	All patients (N=264) n(%) nae
Congenital, familial and genetic disorders	43 (52.4%) 62	67 (39.2%) 83	110 (43.5%) 145	53 (58.9%) 69	87 (50.0%) 107	140 (53.0%) 176
Patent ductus arteriosus	43 (52.4%) 62	66 (38.6%) 82	109 (43.1%) 144	53 (58.9%) 69	87 (50.0%) 106	140 (53.0%) 175
Metabolism and nutrition disorders	44 (53.7%) 88	63 (36.8%) 128	107 (42.3%) 216	53 (58.9%) 108	56 (32.2%) 119	109 (41.3%) 227
Hyperglycaemia	44 (53.7%) 77	63 (36.8%) 108	107 (42.3%) 185	53 (58.9%) 89	56 (32.2%) 98	109 (41.3%) 187
Glucose tolerance impaired	7 (8.5%) 7	8 (4.7%) 8	15 (5.9%) 15	9 (10.0%) 9	7 (4.0%) 7	16 (6.1%) 16
Increased insulin requirement	3 (3.7%) 3	9 (5.3%) 10	12 (4.7%) 13	6 (6.7%) 6	11 (6.3%) 12	17 (6.4%) 18
Nervous system disorders	29 (35.4%) 46	33 (19.3%) 46	62 (24.5%) 92	36 (40.0%) 55	36 (20.7%) 51	72 (27.3%) 106
Intraventricular haemorrhage	29 (35.4%) 45	32 (18.7%) 43	61 (24.1%) 88	34 (37.8%) 49	36 (20.7%) 48	70 (26.5%) 97
Infections and infestations	30 (36.6%) 45	32 (18.7%) 46	62 (24.5%) 91	25 (27.8%) 31	39 (22.4%) 49	64 (24.2%) 80
Sepsis neonatal	24 (29.3%) 25	28 (16.4%) 31	52 (20.6%) 56	19 (21.1%) 20	34 (19.5%) 34	53 (20.1%) 54
Staphylococcal sepsis	4 (4.9%) 4	5 (2.9%) 6	9 (3.6%) 10	1 (1.1%) 1	3 (1.7%) 3	4 (1.5%) 4
Respiratory, thoracic and mediastinal disorders	13 (15.9%) 27	29 (17.0%) 63	42 (16.6%) 90	21 (23.3%) 34	35 (20.1%) 64	56 (21.2%) 98
Pulmonary arterial hypertension	5 (6.1%) 8	13 (7.6%) 21	18 (7.1%) 29	11 (12.2%) 16	14 (8.0%) 24	25 (9.5%) 40
Pulmonary haemorrhage	7 (8.5%) 13	14 (8.2%) 22	21 (8.3%) 35	6 (6.7%) 9	16 (9.2%) 24	22 (8.3%) 33
Vascular disorders	13 (15.9%) 22	15 (8.8%) 21	28 (11.1%) 43	14 (15.6%) 23	19 (10.9%) 34	33 (12.5%) 57
Hypotension	13 (15.9%) 22	15 (8.8%) 21	28 (11.1%) 43	13 (14.4%) 21	17 (9.8%) 30	30 (11.4%) 51
Surgical and medical procedures	3 (3.7%) 3	11 (6.4%) 11	14 (5.5%) 14	8 (8.9%) 9	12 (6.9%) 13	20 (7.6%) 22
Inhalation therapy	3 (3.7%) 3	10 (5.8%) 10	13 (5.1%) 13	8 (8.9%) 8	8 (4.6%) 8	16 (6.1%) 16
Renal and urinary disorders	2 (2.4%) 2	6 (3.5%) 6	8 (3.2%) 8	8 (8.9%) 9	7 (4.0%) 7	15 (5.7%) 16
Gastrointestinal disorders	5 (6.1%) 10	8 (4.7%) 18	13 (5.1%) 28	5 (5.6%) 8	4 (2.3%) 7	9 (3.4%) 15
Cardiac disorder	3 (3.7%) 4	2 (1.2%) 3	5 (2.0%) 7	6 (6.7%) 8	5 (2.9%) 5	11 (4.2%) 13

N = Number of patients within the group, n = Number of patients within the category, nae = Number of adverse events. HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-

Table 15: Most common (in ≥ 5% of patients) SAEs between D1 and D10 (on treatment period) by gestational age (SAF)

System organ Class/ Adverse events (in ≥ 5% of patients)	HCHS (N=253)						Placebo (N=264)					
	Any AE			SAEs			Any AE			SAEs		
	<26.0 Wks PMA (N = 82) n (%) nae	>=26.0 Wks PMA (N = 171) n(%) nae	All patients (N=253) n(%) nae	<26.0 Wks PMA (N = 82) n (%) nae	>=26.0 Wks PMA (N = 171) n(%) nae	All patients (N=253) n(%) nae	<26.0 Wks PMA (N = 90) n (%) nae	>=26.0 Wks PMA (N = 174) n(%) nae	All patients (N=264) n(%) nae	<26.0 Wks PMA (N = 90) n (%) nae	>=26.0 Wks PMA (N = 174) n(%) nae	All patients (N=264) n(%) nae
Infections and infestations	36 (43.9%) 59	81 (47.4%) 128	117 (46.2%) 187	19 (23.2%) 22	36 (21.1%) 42	55 (21.7%) 64	38 (42.2%) 53	59 (33.9%) 111	97 (36.7%) 164	15 (16.7%) 17	32 (18.4%) 37	47 (17.8%) 54
Sepsis neonatal	30 (36.6%) 33	67 (39.2%) 77	97(38.3%) 110	-	-	-	31 (34.4%) 35	57 (32.8%) 71	88 (33.3%) 106	-	-	-
Sepsis	4 (4.9%) 4	11 (6.4%) 11	15 (9%) 15	4 (4.9%) 4	11 (6.4%) 11	15 (5.9%) 15	3 (3.3%) 3	9 (5.2%) 10	12 (4.5%) 13	3 (3.3%) 3	9 (5.2%) 10	12 (4.5%) 13
Septic shock	6 (7.3%) 6	10 (5.8%) 10	16 (6.3%) 16	6 (7.3%) 6	10 (5.8%) 10	16 (6.3%) 16	5 (5.6%) 5	5 (2.9%) 5	10 (3.8%) 10	5 (5.6%) 5	5 (2.9%) 5	10 (3.8%) 10
Staphylococcal sepsis	4 (4.9%) 4	9 (5.3%) 9	13 (5.1%) 13	4 (4.9%) 4	9 (5.3%) 9	13 (5.1%) 13	1 (1.1%) 1	10 (5.7%) 10	11 (4.2%) 11	1 (1.1%) 1	10 (5.7%) 10	11 (4.2%) 11
Congenital, familial and genetic disorders	26 (31.7%) 28	32 (18.7%) 42	58 (22.9%) 70	1 (1.2%) 1	3 (1.8%) 3	4 (1.6%) 4	36 (40.0%) 41	35 (20.1%) 44	71 (26.9%) 85	4 (4.4%) 4	2 (1.1%) 2	6 (2.3%) 6
Patent ductus arteriosus	25 (30.5%) 27	31 (18.1%) 41	56 (22.1%) 68	0 (0%) 0	2 (1.2%) 2	2 (0.8%) 2	35 (38.9%) 39	35 (20.1%) 44	70 (26.5%) 83	3 (3.3%) 3	2 (1.1%) 2	5 (1.9%) 5
Surgical and medical procedures	19 (23.2%) 22	25 (14.6%) 28	44 (17.4%) 50	17 (20.7%) 17	19 (11.1%) 19	36 (14.2%) 36	33 (36.7%) 34	24 (13.8%) 25	57 (21.6%) 59	30 (33.3%) 30	21 (12.1%) 21	51 (19.3%) 51
Patent ductus arteriosus repair	15 (18.3%) 15	18 (10.5%) 18	33 (13.0%) 33	15 (18.3%) 15	18 (10.5%) 18	33 (13.0%) 33	29 (32.2%) 29	21 (12.1%) 21	50 (18.9%) 50	29 (32.2%) 29	21 (12.1%) 21	50 (18.9%) 50
Inhalation therapy	5 (6.1%) 5	8 (4.7%) 9	13 (5.1%) 14	-	-	-	3 (3.3%) 3	4 (2.3%) 4	7 (2.7%) 7	-	-	-
Respiratory, thoracic and mediastinal disorders	19 (23.2%) 35	23 (13.5%) 41	42 (16.6%) 76	18 (22.0%) 23	22 (12.9%) 30	40 (15.8%) 53	25 (27.8%) 43	20 (11.5%) 28	45 (17.0%) 71	21 (23.3%) 27	16 (9.2%) 17	37 (14.0%) 44
Pulmonary arterial hypertension	9 (11.0%) 18	8 (4.7%) 15	17 (6.7%) 33	9 (11.0%) 9	7 (4.1%) 8	16 (6.3%) 17	8 (8.9%) 13	9 (5.2%) 15	17 (6.4%) 28	6 (6.7%) 6	7 (4.0%) 7	13 (4.9%) 13
Respiratory depression	3 (3.7%) 3	9 (5.3%) 9	12 (4.7%) 12	3 (3.7%) 3	9 (5.3%) 9	12 (4.7%) 12	2 (2.2%) 2	5 (2.9%) 5	7 (2.7%) 7	2 (2.2%) 2	5 (2.9%) 5	7 (2.7%) 7
Hypoxia	6 (7.3%) 7	4 (2.3%) 4	10 (4.0%) 11	5 (6.1%) 5	4 (2.3%) 4	9 (3.6%) 9	6 (6.7%) 6	1 (0.6%) 1	7 (2.7%) 7	6 (6.7%) 6	1 (0.6%) 1	7 (2.7%) 7
Nervous system disorders	17 (20.7%) 26	28 (16.4%) 41	45 (17.8%) 67	12 (14.6%) 12	12 (7.0%) 14	24 (9.5%) 26	19 (21.1%) 27	18 (10.3%) 25	37 (14.0%) 52	14 (15.6%) 16	8 (4.6%) 8	22 (8.3%) 24
Intraventricular haemorrhage	15 (18.3%) 21	23 (13.5%) 30	38 (15.0%) 51	8 (9.8%) 8	6 (3.5%) 6	14 (5.5%) 14	12 (13.3%) 16	13 (7.5%) 16	25 (9.5%) 32	9 (10.0%) 9	3 (1.7%) 3	12 (4.5%) 12
Gastrointestinal disorders	13 (15.9%) 26	18 (10.5%) 33	31 (12.3%) 59	9 (11.0%) 12	12 (7.0%) 16	21 (8.3%) 28	6 (6.7%) 10	15 (8.6%) 30	21 (8.0%) 40	4 (4.4%) 5	12 (6.9%) 17	16 (6.1%) 22
Necrotising colitis	7 (8.5%) 12	10 (5.8%) 17	17 (6.7%) 29	5 (6.1%) 6	7 (4.1%) 7	12 (4.7%) 13	1 (1.1%) 2	10 (5.7%) 18	11 (4.2%) 20	1 (1.1%) 1	8 (4.6%) 8	9 (3.4%) 9
General disorders and administration site conditions	5 (6.1%) 5	9 (5.3%) 9	14 (5.5%) 14	4 (4.9%) 4	7 (4.1%) 7	11 (4.3%) 11	8 (8.9%) 10	9 (5.2%) 10	17 (6.4%) 20	7 (7.8%) 9	8 (4.6%) 9	15 (5.7%) 18
Multi-organ failure	2 (2.4%) 2	3 (1.8%) 3	5 (2.0%) 5	2 (2.4%) 2	3 (1.8%) 3	5 (2.0%) 5	5 (5.6%) 6	2 (1.1%) 2	7 (2.7%) 8	5 (5.6%) 6	2 (1.1%) 2	7 (2.7%) 8
Metabolism and nutrition disorders	7 (8.5%) 12	8 (4.7%) 15	15 (5.9%) 27	7 (8.5%) 8	7 (4.1%) 9	14 (5.5%) 17	6 (6.7%) 9	10 (5.7%) 17	16 (6.1%) 26	5 (5.6%) 5	9 (5.2%) 9	14 (5.3%) 14
Hyperglycaemia	5 (6.1%) 6	7 (4.1%) 10	12 (4.7%) 16	2 (2.4%) 2	4 (2.3%) 4	6 (2.4%) 6	6 (6.7%) 8	9 (5.2%) 15	15 (5.7%) 23	4 (4.4%) 4	7 (4.0%) 7	11 (4.2%) 11
Vascular disorders	6 (7.3%) 7	9 (5.3%) 10	15 (5.9%) 17	2 (2.4%) 3	3 (1.8%) 3	5 (2.0%) 6	5 (5.6%) 7	11 (6.3%) 12	16 (6.1%) 19	3 (3.3%) 3	5 (2.9%) 5	8 (3.0%) 8
Hypotension	5 (6.1%) 5	6 (3.5%) 7	11 (4.3%) 12	1 (1.2%) 1	1 (0.6%) 1	2 (0.8%) 2	4 (4.4%) 6	9 (5.2%) 10	13 (4.9%) 16	2 (2.2%) 2	3 (1.7%) 3	5 (1.9%) 5
Cardiac disorder	2 (2.4%) 2	5 (2.9%) 5	7 (2.8%) 7	2 (2.4%) 2	5 (2.9%) 5	7 (2.8%) 7	11 (12.2%) 12	2 (1.1%) 3	13 (4.9%) 15	11 (12.2%) 11	2 (1.1%) 2	13 (4.9%) 13
Cardio-respiratory arrest	0 (0%) 0	1 (0.6%) 1	1 (0.4%) 1	0 (0%) 0	1 (0.6%) 1	1 (0.4%) 1	6 (6.7%) 6	0 (0%) 0	6 (2.3%) 6	6 (6.7%) 6	0 (0%) 0	6 (2.3%) 6

N = Number of patients within the group, n = Number of patients within the category, nae = Number of adverse events. HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-Menstrual Age

At least one TEAE was reported for 97.6% of HC subjects and 100% placebo subjects in case of delivery < 26 weeks of gestation and for 86.0% HC subjects and 93.7% placebo subjects in case of delivery ≥ 26 weeks of gestation.

During the **on-treatment period (D1-D10)** a higher proportion in the HCHS group of infants born < 26 wks PMA compared to placebo reports **sepsis** events i.e., PT "sepsis neonatal" (29.3% vs 21.1%) and the PT "staphylococcal sepsis" (4.9% vs 1.1%).

During the off-treatment period (D11- up to week 36 PMA) a higher proportion of all patients in the HCHS group compared with placebo reported NEC (6.7% vs 4.2%), Gastrointestinal perforations (2.4% vs 0.4%) and intraventricular haemorrhage (15.% vs 9.5%). For NEC the difference is largest among infants born < 26 wks PMA (HCHS: 8.5% in vs 1.1% with placebo).

3.3.9.4. Adverse drug reactions

No presentation of TEAEs identified as adverse drug reactions (ADRs) has been identified by the applicant.

In PREMILOC only SAEs, but not AEs in general, were assessed as related to study drug or not. Therefore, the applicant instead proposes to include the ADRs reported with $\geq$ 2% (i.e, a difference by approximately 5 patients) in the HCHS group compared to placebo in PREMILOC in Table 1 in SmPC section 4.8. This approach is acknowledged. However, any potential rational for anuria to be a higher risk for the HCHS group should be discussed.

Table 16: Adverse reactions from clinical trial PREMILOC

System organ class	Adverse reactions	Frequency
Infections and infestations	Sepsis neonatal	Very common
	Septic shock	Common
Nervous system disorders	Intraventricular haemorrhage	Very common
Respiratory, thoracic and mediastinal disorders	Respiratory depression	Common
Gastrointestinal disorders	Necrotising colitis	Common
	Gastrointestinal perforation	Common
Renal and urinary disorders	Anuria	Common

3.3.9.5. Serious adverse event/deaths/other significant events

Serious TEAEs are presented in the below table.

Table 17: Serious TEAEs by system organ class (SAF)

MedDRA (V18.0) System Organ Class Preferred Term	NCHS (N = 253) n (%) nae	Placebo (N = 264) n (%) nae
Any Serious TEAE	191 (75.5%) 591	201 (76.1%) 587
Metabolism and nutrition disorders	114 (45.1%) 132	114 (43.2%) 130
Infections and infestations	85 (33.6%) 102	66 (25.0%) 77
Respiratory, thoracic and mediastinal disorders	72 (28.5%) 109	76 (28.8%) 101
Surgical and medical procedures	40 (15.8%) 40	58 (22.0%) 58
Nervous system disorders	47 (18.6%) 56	50 (18.9%) 60
Intraventricular haemorrhage	38 (15.0%) 38	40 (15.2%) 40
Gastrointestinal disorders	31 (12.3%) 44	25 (9.5%) 33
Vascular disorders	21 (8.3%) 22	31 (11.7%) 34
Cardiac disorders	12 (4.7%) 15	26 (9.8%) 28
General disorders and administration site conditions	17 (6.7%) 19	21 (8.0%) 24
Renal and urinary disorders	15 (5.9%) 15	18 (6.8%) 19
Congenital, familial and genetic disorders	11 (4.3%) 11	13 (4.9%) 13
Eye disorders	5 (2.0%) 5	2 (0.8%) 2
Investigations	3 (1.2%) 10	4 (1.5%) 4

N = Number of subjects within the group, n = Number of subjects within the category, nae = Number of adverse events. TEAE = Treatment-Emergent Adverse Event, HCHS = Hydrocortisone Hemisuccinate, Ordering of MedDRA System Organ Class based on descending frequency of subjects with events in the total population

Table 18: Most common (in ⩾ 5% of patients) SAEs between D1 and D10 (on treatment period) by gestational age (SAF)

System organ Class/ Adverse events (in ≥ 5% of patients)	HCHS (N=253) SAEs <26.0 Wks PMA (N = 82) n (%) nae	HCHS (N=253) SAEs >=26.0 Wks PMA (N = 171) n(%) nae	HCHS (N=253) SAEs All patients (N=253) n(%) nae	Placebo (N=264) SAEs <26.0 Wks PMA (N = 90) n (%) nae	Placebo (N=264) SAEs >=26.0 Wks PMA (N = 174) n(%) nae	Placebo (N=264) SAEs All patients (N=264) n(%) nae
Congenital, familial and genetic disorders	5 (6.1%) 5	2 (1.2%) 2	7 (2.8%) 7	1 (1.1%) 1	4 (2.3%) 4	5 (1.9%) 5
Patent ductus arteriosus	5 (6.1%) 5	2 (1.2%) 2	7 (2.8%) 7	1 (1.1%) 1	3 (1.7%) 3	4 (1.5%) 4
Metabolism and nutrition disorders	44 (53.7%) 46	61 (35.7%) 66	105 (41.5%) 112	52 (57.8%) 57	55 (31.6%) 59	107 (40.5%) 116
Hyperglycaemia	34 (41.5%) 35	44 (25.7%) 46	78 (30.8%) 81	37 (41.1%) 38	38 (21.8%) 39	75 (28.4%) 77
Glucose tolerance impaired	7 (8.5%) 7	8 (4.7%) 8	15 (5.9%) 15	9 (10.0%) 9	7 (4.0%) 7	16 (6.1%) 16
Increased insulin requirement	3 (3.7%) 3	9 (5.3%) 10	12 (4.7%) 13	6 (6.7%) 6	11 (6.3%) 12	17 (6.4%) 18
Nervous system disorders	15 (18.3%) 15	12 (7.0%) 12	27 (10.7%) 27	16 (17.8%) 18	14 (8.0%) 17	30 (11.4%) 35
Intraventricular haemorrhage	14 (17.1%) 14	10 (5.8%) 10	24 (9.5%) 24	14 (15.6%) 14	14 (8.0%) 14	28 (10.6%) 28
Infections and infestations	16 (19.5%) 17	12 (7.0%) 12	28 (11.1%) 29	7 (7.8%) 8	12 (6.9%) 13	19 (7.2%) 21
Sepsis neonatal	4 (4.9%) 4	4 (2.3%) 4	8 (3.2%) 8	1 (1.1%) 1	3 (1.7%) 3	4 (1.5%) 4
Staphylococcal sepsis	4 (4.9%) 4	5 (2.9%) 5	9 (3.6%) 9	0 (0%) 0	3 (1.7%) 3	3 (1.1%) 3
Respiratory, thoracic and mediastinal disorders	12 (14.6%) 15	26 (15.2%) 33	38 (15.0%) 48	15 (16.7%) 17	28 (16.1%) 33	43 (16.3%) 50
Pulmonary arterial hypertension	4 (4.9%) 4	8 (4.7%) 8	12 (4.7%) 12	7 (7.8%) 7	11 (6.3%) 11	18 (6.8%) 18
Pulmonary haemorrhage	6 (7.3%) 6	10 (5.8%) 10	16 (6.3%) 16	3 (3.3%) 3	9 (5.2%) 9	12 (4.5%) 12
Vascular disorders	8 (9.8%) 8	8 (4.7%) 8	16 (6.3%) 16	12 (13.3%) 12	14 (8.0%) 14	26 (9.8%) 26
Hypotension	8 (9.8%) 8	8 (4.7%) 8	16 (6.3%) 16	11 (12.2%) 11	12 (6.9%) 12	23 (8.7%) 23
Surgical and medical procedures						
Inhalation therapy						
Renal and urinary disorders	2 (2.4%) 2	6 (3.5%) 6	8 (3.2%) 8	8 (8.9%) 9	6 (3.4%) 6	14 (5.3%) 15
Gastrointestinal disorders	3 (3.7%) 5	7 (4.1%) 10	10 (4.0%) 15	5 (5.6%) 6	3 (1.7%) 3	8 (3.0%) 9
Cardiac disorder	3 (3.7%) 3	2 (1.2%) 3	5 (2.0%) 6	6 (6.7%) 7	5 (2.9%) 5	11 (4.2%) 12

N = Number of patients within the group, n = Number of patients within the category, nae = Number of adverse events. HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-

Table 19: Most common (in ⩾ 5% of patients) SAEs between D11 and W36 of PMA (off treatment period) by gestational age (SAF)

System organ Class/ Adverse events (in ≥ 5% of patients)	HCHS (N=253)			Placebo (N=264)		
	SAEs			SAEs		
	<26.0 Wks PMA (N = 82) n (%) nae	>=26.0 Wks PMA (N = 171) n(%) nae	All patients (N=253) n(%) nae	<26.0 Wks PMA (N = 90) n (%) nae	>=26.0 Wks PMA (N = 174) n(%) nae	All patients (N=264) n(%) nae
Infections and infestations	19 (23.2%) 22	36 (21.1%) 42	55 (21.7%) 64	15 (16.7%) 17	32 (18.4%) 37	47 (17.8%) 54
Sepsis neonatal	-	-	-	-	-	-
Sepsis	4 (4.9%) 4	11 (6.4%) 11	15 (5.9%) 15	3 (3.3%) 3	9 (5.2%) 10	12 (4.5%) 13
Septic shock	6 (7.3%) 6	10 (5.8%) 10	16 (6.3%) 16	5 (5.6%) 5	5 (2.9%) 5	10 (3.8%) 10
Staphylococcal sepsis	4 (4.9%) 4	9 (5.3%) 9	13 (5.1%) 13	1 (1.1%) 1	10 (5.7%) 10	11 (4.2%) 11
Congenital, familial and genetic disorders	1 (1.2%) 1	3 (1.8%) 3	4 (1.6%) 4	4 (4.4%) 4	2 (1.1%) 2	6 (2.3%) 6
Patent ductus arteriosus	0 (0%) 0	2 (1.2%) 2	2 (0.8%) 2	3 (3.3%) 3	2 (1.1%) 2	5 (1.9%) 5
Surgical and medical procedures	17 (20.7%) 17	19 (11.1%) 19	36 (14.2%) 36	30 (33.3%) 30	21 (12.1%) 21	51 (19.3%) 51
Patent ductus arteriosus repair	15 (18.3%) 15	18 (10.5%) 18	33 (13.0%) 33	29 (32.2%) 29	21 (12.1%) 21	50 (18.9%) 50
Inhalation therapy	-	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	18 (22.0%) 23	22 (12.9%) 30	40 (15.8%) 53	21 (23.3%) 27	16 (9.2%) 17	37 (14.0%) 44
Pulmonary arterial hypertension	9 (11.0%) 9	7 (4.1%) 8	16 (6.3%) 17	6 (6.7%) 6	7 (4.0%) 7	13 (4.9%) 13
Respiratory depression	3 (3.7%) 3	9 (5.3%) 9	12 (4.7%) 12	2 (2.2%) 2	5 (2.9%) 5	7 (2.7%) 7
Hypoxia	5 (6.1%) 5	4 (2.3%) 4	9 (3.6%) 9	6 (6.7%) 6	1 (0.6%) 1	7 (2.7%) 7
Nervous system disorders	12 (14.6%) 12	12 (7.0%) 14	24 (9.5%) 26	14 (15.6%) 16	8 (4.6%) 8	22 (8.3%) 24
Intraventricular haemorrhage	8 (9.8%) 8	6 (3.5%) 6	14 (5.5%) 14	9 (10.0%) 9	3 (1.7%) 3	12 (4.5%) 12
Gastrointestinal disorders	9 (11.0%) 12	12 (7.0%) 16	21 (8.3%) 28	4 (4.4%) 5	12 (6.9%) 17	16 (6.1%) 22
Necrotising colitis	5 (6.1%) 6	7 (4.1%) 7	12 (4.7%) 13	1 (1.1%) 1	8 (4.6%) 8	9 (3.4%) 9
General disorders and administration site conditions	4 (4.9%) 4	7 (4.1%) 7	11 (4.3%) 11	7 (7.8%) 9	8 (4.6%) 9	15 (5.7%) 18
Multi-organ failure	2 (2.4%) 2	3 (1.8%) 3	5 (2.0%) 5	5 (5.6%) 6	2 (1.1%) 2	7 (2.7%) 8
Metabolism and nutrition disorders	7 (8.5%) 8	7 (4.1%) 9	14 (5.5%) 17	5 (5.6%) 5	9 (5.2%) 9	14 (5.3%) 14
Hyperglycaemia	2 (2.4%) 2	4 (2.3%) 4	6 (2.4%) 6	4 (4.4%) 4	7 (4.0%) 7	11 (4.2%) 11
Vascular disorders	2 (2.4%) 3	3 (1.8%) 3	5 (2.0%) 6	3 (3.3%) 3	5 (2.9%) 5	8 (3.0%) 8
Hypotension	1 (1.2%) 1	1 (0.6%) 1	2 (0.8%) 2	2 (2.2%) 2	3 (1.7%) 3	5 (1.9%) 5
Cardiac disorder	2 (2.4%) 2	5 (2.9%) 5	7 (2.8%) 7	11 (12.2%) 11	2 (1.1%) 2	13 (4.9%) 13
Cardio-respiratory arrest	0 (0%) 0	1 (0.6%) 1	1 (0.4%) 1	6 (6.7%) 6	0 (0%) 0	6 (2.3%) 6

N = Number of patients within the group, n = Number of patients within the category, nae = Number of adverse events. HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-Menstrual Age

At least one SAE was reported for 92.7% of HC subjects and 91.1% of placebo subjects delivered before 26 weeks of gestation, and for 67.3% of HC subjects and 43.2% of placebo subjects delivered ≥ 26 weeks of gestation.

During the **on-treatment period** and **the off-treatment period**, a slightly higher proportion of **sepsis related SAE PTs** was noted for the HCHS group compared to placebo. During the off-treatment period also a difference in sepsis related PTs was noted but also for the **PT Necrotizing colitis (SAEs)** especially in the younger birth age population (HCHS: 6.1% vs placebo: 1.1%).

Severe serious TEAEs, reported in 75.5% of HCHS subjects and 76.1% of placebo subjects, are presented by system organ class in Table 18.

Table 20: Severe Serious TEAEs reported by System Organ Class (SAF)

MedDRA (V18.0) System Organ Class Preferred Term	HCHS N=253 n (%)	Placebo N=264 n (%)
Any Severe Serious TEAE	138 (55%)	136 (52%)
Infections and infestations	62 (25%)	47 (18%)
Respiratory, thoracic and mediastinal disorders	52 (21%)	51 (19%)
Metabolism and nutrition disorders	37 (15%)	30 (11%)
Nervous system disorders	37 (15%)	41 (16%)
Surgical and medical procedures	23 (9.1%)	32 (12%)
Gastrointestinal disorders	21 (8.3%)	14 (5.3%)
Vascular disorders	13 (5.1%)	21 (8.0%)
Cardiac disorders	10 (4.0%)	23 (8.7%)
General disorders and administration site conditions	12 (4.7%)	13 (4.9%)
Renal and urinary disorders	9 (3.6%)	10 (3.8%)
Congenital, familial and genetic disorders	8 (3.2%)	9 (3.4%)
Renal and urinary disorders	9 (3.6%)	10 (3.8%)
Congenital, familial and genetic disorders	8 (3.2%)	9 (3.4%)
Eye disorders	3 (1.2%)	1 (0.4%)
Investigations	1 (0.4%)	1 (0.4%)

N = Number of subjects within the group, n = Number of subjects within the category.
TEAE = Treatment-Emergent Adverse Event, HCHS = Hydrocortisone Hemisuccinate.
Missing severities are considered as 'severe'.
Ordering of MedDRA System Organ Class is based on descending frequency of subjects with events in the total population

Severe SAE were reported for 72% of HC subjects vs 73% of placebo subjects for subjects delivered < 26 weeks of gestation and for 46% of HC subjects vs 40% of placebo subjects for subjects delivered ≥ 26 weeks of gestation.

Serious TEAEs considered as related are presented in Table 19.

Table 21: Serious TEAEs considered as related to Study Treatment According to the Investigator, by SOC (SAF)

MedDRA (V18.0) System Organ Class Preferred Term	HCHS (N = 253) n (%) nae	Placebo (N = 264) n (%) nae
Any Serious TEAE Related to Study Treatment According to the Investigator	14 (5.5%) 18	12 (4.5%) 16
Metabolism and nutrition disorders	10 (4.0%) 11	11 (4.2%) 11
Gastrointestinal disorders	3 (1.2%) 4	0 (0%) 0
Nervous system disorders	2 (0.8%) 2	0 (0%) 0
Cardiac disorders	0 (0%) 0	1 (0.4%) 1
General disorders and administration site conditions	0 (0%) 0	1 (0.4%) 1
Infections and infestations	0 (0%) 0	1 (0.4%) 1
Injury, poisoning and procedural complications	0 (0%) 0	1 (0.4%) 1
Renal and urinary disorders	1 (0.4%) 1	0 (0%) 0
Respiratory, thoracic and mediastinal disorders	0 (0%) 0	1 (0.4%) 1

N = Number of subjects within the group, n = Number of subjects within the category, nae = Number of adverse events. TEAE = Treatment-Emergent Adverse Event, HCHS = Hydrocortisone Hemisuccinate. Ordering of MedDRA System Organ Class is based on descending frequency of subjects with events in the total population

Fatal events

During the **on-treatment period** there was no difference in proportion of infants with fatal events between the two treatment groups. However, in infants born < 26 wks PMA fatal events were more commonly reported in the HCHS group (24.4%) compared to placebo (16.7%). The difference was driven by IVH events. In the <26 wks PMA HCHS group 50% (10/20 cases) of the fatal events included the PT IVH compared to 27% (4 /15 cases) in the<26 wks PMA placebo group. Fatal events were less common in the HCHS treated ≥ 26 wks PMA group compared to placebo (4.7% vs 8.6%).

During the **off-treatment period** (D11-w36 PMA) a slightly higher proportion in the placebo group reported any fatal event (13.6%) compared to the HCHS group (11.5%). No specific fatal PT pattern regarding was noted.

Adverse events of special interest

- **PREMILOC**

Adverse events of special interest, as described in the additional SAP, are described in Table 23.

Adverse events of special interest (AESI) between D1 and D10 (SAF), is described in Table xd.

Adverse events of special interest (AESI) between D11 and W36 of PMA (SAF), is described in Table xe.

During the on-treatment period late onset sepsis or systemic candida infections were reported by a larger proportion of patients in infants born before 26 weeks HCHS group compared to placebo (30.5% vs 20.0%). On the other hand, pulmonary hypertension AESI was less commonly reported in the HCHS lower birth age group (6.1%) compared to placebo (12.2%). See table xd.

During the off treatment period a slightly higher proportion in the HCHS overall age group compared to placebo reported NEC (6.7% vs 4.2%), GI perforation (2.8% vs 1.5%), severe IVH (6.3% vs 4.5%) and late systemic candida infection (43.1% vs 35.6%). On the other hand, PDA ligation was less commonly reported in the HCHS group (13.0%) compared to placebo (18.9%). See Table 20.

Table 22: Adverse events of special interest

	HCHS (N = 253) n (%)	Placebo (N = 264) n (%)
Any Early Respiratory Complication	28/253 (11.1%)	30/264 (11.4%)
Air Leaks	5/253 (2.0%)	8/264 (3.0%)
Pulmonary Haemorrhage	26/253 (10.3%)	28/264 (10.6%)
Pulmonary Hypertension	36/253 (14.2%)	44/264 (16.7%)
Necrotizing enterocolitis	19/253 (7.5%)	13/264 (4.9%)
Patent Ductus Arteriosus Ligation	37/253 (14.6%)	56/264 (21.2%)
Gastrointestinal Perforation	14/253 (5.5%)	10/264 (3.8%)
Severe Intraventricular Haemorrhage before 40 weeks of PMA	41/253 (16.2%)	42/264 (15.9%)
Periventricular Leukomalacia	3/253 (1.2%)	11/264 (4.2%)
Late-Onset Sepsis or Systemic Candida Infection	139/253 (54.9%)	121/264 (45.8%)
Late-Onset Systemic Candida Infection	6/253 (2.4%)	8/264 (3.0%)
Insulin Requirement During First Two Weeks of Life	111/253 (43.9%)	114/264 (43.2%)
Cerebral White Matter Lesions	0/253 (0%)	0/264 (0%)
Haemodynamic Failure	2/253 (0.8%)	3/264 (1.1%)

N = Number of subjects within the group, n = Number of subjects within the category, n' = Number of subjects with an available assessment within the group. Percentages are calculated with respect to the number of subjects with an available assessment within the group. TEAE = Treatment-Emergent Adverse Event, HCHS = Hydrocortisone Hemisuccinate

14.3 SAFETY DATA
14.3.1 Adverse Events
14.3.1.1 Safety Set
14.3.1.1.3 TEAEs of Special Interest
14.3.1.1.3.1 Summary

Variable	HCHS			Placebo		
	<26.0 Wks PMA (N = 82) n/n' (%)	>=26.0 Wks PMA (N = 171) n/n' (%)	All Patients (N = 253) n/n' (%)	<26.0 Wks PMA (N = 90) n/n' (%)	>=26.0 Wks PMA (N = 174) n/n' (%)	All Patients (N = 264) n/n' (%)
Any Early Respiratory Complication	7/ 82 (8.5%)	21/171 (12.3%)	28/253 (11.1%)	9/ 90 (10.0%)	21/174 (12.1%)	30/264 (11.4%)
Air Leaks	0/ 82 (0%)	5/171 (2.9%)	5/253 (2.0%)	6/ 90 (6.7%)	2/174 (1.1%)	8/264 (3.0%)
Pulmonary Haemorrhage	9/ 82 (11.0%)	17/171 (9.9%)	26/253 (10.3%)	11/ 90 (12.2%)	17/174 (9.8%)	28/264 (10.6%)
Pulmonary Hypertension	14/ 82 (17.1%)	22/171 (12.9%)	36/253 (14.2%)	20/ 90 (22.2%)	24/174 (13.8%)	44/264 (16.7%)
Necrotizing Colitis	7/ 82 (8.5%)	12/171 (7.0%)	19/253 (7.5%)	2/ 90 (2.2%)	11/174 (6.3%)	13/264 (4.9%)
Patent Ductus Arteriosus Ligation	17/ 82 (20.7%)	20/171 (11.7%)	37/253 (14.6%)	30/ 90 (33.3%)	26/174 (14.9%)	56/264 (21.2%)
Gastrointestinal Perforation	6/ 82 (7.3%)	8/171 (4.7%)	14/253 (5.5%)	6/ 90 (6.7%)	4/174 (2.3%)	10/264 (3.8%)
Severe Intraventricular Haemorrhage before 40 weeks PMA	23/ 82 (28.0%)	18/171 (10.5%)	41/253 (16.2%)	25/ 90 (27.8%)	17/174 (9.8%)	42/264 (15.9%)
Periventricular Leukomalacia	0/ 82 (0%)	3/171 (1.8%)	3/253 (1.2%)	6/ 90 (6.7%)	5/174 (2.9%)	11/264 (4.2%)
Late-Onset Sepsis or Systemic Candida Infection	53/ 82 (64.6%)	86/171 (50.3%)	139/253 (54.9%)	49/ 90 (54.4%)	72/174 (41.4%)	121/264 (45.8%)
Late-Onset Systemic Candida Infection	4/ 82 (4.9%)	2/171 (1.2%)	6/253 (2.4%)	5/ 90 (5.6%)	3/174 (1.7%)	8/264 (3.0%)
Insulin Requirement During First Two Weeks of Life	45/ 82 (54.9%)	66/171 (38.6%)	111/253 (43.9%)	55/ 90 (61.1%)	59/174 (33.9%)	114/264 (43.2%)
Cerebral White Matter Lesions	0/ 82 (0%)	0/171 (0%)	0/253 (0%)	0/ 90 (0%)	0/174 (0%)	0/264 (0%)
Haemodynamic Failure	2/ 82 (2.4%)	0/171 (0%)	2/253 (0.8%)	2/ 90 (2.2%)	1/174 (0.6%)	3/264 (1.1%)

Table 23: Adverse events of special interest (AESI) between D1 and D10 (SAF)

	HCHS			Placebo		
Variable	**<26.0 Wks PMA (N = 82) n/n' (%)**	**≥26.0 Wks PMA (N = 171) n/n' (%)**	**All subjects (N = 253) n/n' (%)**	**<26.0 Wks PMA (N = 90) n/n' (%)**	**≥26.0 Wks PMA (N = 174) n/n' (%)**	**All subjects (N = 264) n/n' (%)**
Any Early Respiratory Complication	6/ 82 (7.3%)	21/171 (12.3%)	27/253 (10.7%)	7/ 90 (7.8%)	21/174 (12.1%)	28/264 (10.6%)
Air Leaks	0/ 82 (0%)	4/171 (2.3%)	4/253 (1.6%)	2/ 90 (2.2%)	1/174 (0.6%)	3/264 (1.1%)
Pulmonary Haemorrhage	7/ 82 (8.5%)	15/171 (8.8%)	22/253 (8.7%)	6/ 90 (6.7%)	16/174 (9.2%)	22/264 (8.3%)
Pulmonary Hypertension	5/ 82 (6.1%)	13/171 (7.6%)	18/253 (7.1%)	11/ 90 (12.2%)	14/174 (8.0%)	25/264 (9.5%)
Necrotizing Colitis	1/ 82 (1.2%)	1/171 (0.6%)	2/253 (0.8%)	0/ 90 (0%)	0/174 (0%)	0/264 (0%)
Patent Ductus Arteriosus Ligation	1/ 82 (1.2%)	1/171 (0.6%)	2/253 (0.8%)	1/ 90 (1.1%)	3/174 (1.7%)	4/264 (1.5%)
Gastrointestinal Perforation	4/ 82 (4.9%)	4/171 (2.3%)	8/253 (3.2%)	4/ 90 (4.4%)	4/174 (2.3%)	8/264 (3.0%)
Severe Intraventricular Haemorrhage before 40 weeks PMA	17/ 82 (20.7%)	10/171 (5.8%)	27/253 (10.7%)	19/ 90 (21.1%)	14/174 (8.0%)	33/264 (12.5%)
Periventricular Leukomalacia	0/ 82 (0%)	1/171 (0.6%)	1/253 (0.4%)	1/ 90 (1.1%)	0/174 (0%)	1/264 (0.4%)
Late-Onset Sepsis or Systemic Candida Infection	25/ 82 (30.5%)	19/171 (11.1%)	44/253 (17.4%)	18/ 90 (20.0%)	20/174 (11.5%)	38/264 (14.4%)
Late-Onset Systemic Candida Infection	4/ 82 (4.9%)	0/171 (0%)	4/253 (1.6%)	2/ 90 (2.2%)	1/174 (0.6%)	3/264 (1.1%)
Insulin Requirement During First Two Weeks of Life/Hyperglycaemia	44/ 82 (53.7%)	63/171 (36.8%)	107/253 (42.3%)	53/ 90 (58.9%)	56/174 (32.2%)	109/264 (41.3%)
Cerebral White Matter Lesions	0/ 82 (0%)	0/171 (0%)	0/253 (0%)	0/ 90 (0%)	0/174 (0%)	0/264 (0%)
Haemodynamic Failure	0/ 82 (0%)	0/171 (0%)	0/253 (0%)	1/ 90 (1.1%)	0/174 (0%)	1/264 (0.4%)

N = Number of patients within the group, n = Number of patients within the category, nae = Number of adverse events. HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-Menstrual Age

Table 24: Adverse events of special interest (AESI) between D11 and W36 of PMA (SAF)

	HCHS			Placebo		
Variable	**<26.0 Wks PMA (N = 82) n/n' (%)**	**≥26.0 Wks PMA (N = 171) n/n' (%)**	**All subjects (N = 253) n/n' (%)**	**<26.0 Wks PMA (N = 90) n/n' (%)**	**≥26.0 Wks PMA (N = 174) n/n' (%)**	**All subjects (N = 264) n/n' (%)**
Any Early Respiratory Complication	1/ 82 (1.2%)	0/171 (0%)	1/253 (0.4%)	2/ 90 (2.2%)	0/174 (0%)	2/264 (0.8%)
Air Leaks	0/ 82 (0%)	1/171 (0.6%)	1/253 (0.4%)	4/ 90 (4.4%)	1/174 (0.6%)	5/264 (1.9%)
Pulmonary Haemorrhage	2/ 82 (2.4%)	2/171 (1.2%)	4/253 (1.6%)	4/ 90 (4.4%)	1/174 (0.6%)	5/264 (1.9%)
Pulmonary Hypertension	9/ 82 (11.0%)	8/171 (4.7%)	17/253 (6.7%)	8/ 90 (8.9%)	9/174 (5.2%)	17/264 (6.4%)
Necrotizing Colitis	7/ 82 (8.5%)	10/171 (5.8%)	17/253 (6.7%)	1/ 90 (1.1%)	10/174 (5.7%)	11/264 (4.2%)
Patent Ductus Arteriosus Ligation	15/ 82 (18.3%)	18/171 (10.5%)	33/253 (13.0%)	29/ 90 (32.2%)	21/174 (12.1%)	50/264 (18.9%)
Gastrointestinal Perforation	3/ 82 (3.7%)	4/171 (2.3%)	7/253 (2.8%)	4/ 90 (4.4%)	0/174 (0%)	4/264 (1.5%)
Severe Intraventricular Haemorrhage before 40 weeks PMA	8/ 82 (9.8%)	8/171 (4.7%)	16/253 (6.3%)	9/ 90 (10.0%)	3/174 (1.7%)	12/264 (4.5%)
Periventricular Leukomalacia	0/ 82 (0%)	3/171 (1.8%)	3/253 (1.2%)	5/ 90 (5.6%)	4/174 (2.3%)	9/264 (3.4%)
Late-Onset Sepsis or Systemic Candida Infection	34/ 82 (41.5%)	75/171 (43.9%)	109/253 (43.1%)	36/ 90 (40.0%)	58/174 (33.3%)	94/264 (35.6%)
Late-Onset Systemic Candida Infection	0/ 82 (0%)	2/171 (1.2%)	2/253 (0.8%)	3/ 90 (3.3%)	2/174 (1.1%)	5/264 (1.9%)
Insulin Requirement During First Two Weeks of Life/Hyperglycaemia	3/ 82 (3.7%)	4/171 (2.3%)	7/253 (2.8%)	4/ 90 (4.4%)	4/174 (2.3%)	8/264 (3.0%)
Cerebral White Matter Lesions	0/ 82 (0%)	0/171 (0%)	0/253 (0%)	0/ 90 (0%)	0/174 (0%)	0/264 (0%)
Haemodynamic Failure	2/ 82 (2.4%)	0/171 (0%)	2/253 (0.8%)	1/ 90 (1.1%)	1/174 (0.6%)	2/264 (0.8%)

N = Number of patients within the group, n = Number of patients within the category, nae = Number of adverse events. HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-Menstrual Age

AESI considered if reported as serious or HIV > grade 2

Safety related to cortisol levels

Cortisol levels are available in 111/172 (64.5%) of the infants born before 26 wks PMA and 223/345 (64.6%) of the infants born ≥ 26 weeks PMA.

No pattern in the overall summary of adverse events (during the whole study) could be noted between subjects with cortisol levels > median at D0 compared to those with a cortisol level ≤ median in the HCHS group or between treatment groups.

During the off treatment period, a higher proportion of infants with cortisol levels > median reports events within the SOC Infections and infestations in the HCHS group (57.1% [infants born < 26 wks PMA] and 55.6% [infants born ≥26 to 36 wks PMA]) compared to those with cortisol levels ≤ median

(36.4% [infants born < 26 wks PMA] and 47.4% [infants born ≥26 to 36 wks PMA]). This pattern is not noted in the placebo group.

During the on-treatment (D1-D10) period, the following AESI are more commonly reported in the HCHS group with cortisol levels > median compared infants with cortisol levels ≤ median: Gastrointestinal Perforation and Severe Intraventricular Haemorrhage before 40 weeks PMA (among infants born < 26 weeks PMA.

During the off-treatment (D11 to week 36 PMA) period the following AESI are more commonly reported in the HCHS group with cortisol levels > median compared infants with cortisol levels ≤ median: Gastrointestinal Perforation, NEC (for infants born < 26 weeks PMA), Late-Onset Sepsis or Systemic Candida, Severe Intraventricular Haemorrhage before 40 weeks PMA and Insulin Requirement During First Two Weeks of Life/Hyperglycaemia.

Table 25: (same as table 35 in the Add CSR) Summary of AESIs On-Treatment (D1 - D10) by Baseline Cortisol Level for Patients with Non-Missing Baseline Cortisol Level

Variable	HCHS				Placebo			
	<26.0 Wks PMA n/n' (%)		>=26.0 Wks PMA n/n' (%)		<26.0 Wks PMA n/n' (%)		>=26.0 Wks PMA n/n' (%)	
	Cortisol <= Median (N = 22)	Cortisol > Median (N = 28)	Cortisol <= Median (N = 57)	Cortisol > Median (N = 54)	Cortisol <= Median (N = 34)	Cortisol > Median (N = 27)	Cortisol <= Median (N = 55)	Cortisol > Median (N = 57)
Any Early Respiratory Complication	2/ 22 (9.1%)	1/ 28 (3.6%)	3/ 57 (5.3%)	8/ 54 (14.8%)	3/ 34 (8.8%)	2/ 27 (7.4%)	5/ 55 (9.1%)	6/ 57 (10.5%)
Air Leaks	0/ 22 (0%)	0/ 28 (0%)	0/ 57 (0%)	3/ 54 (5.6%)	0/ 34 (0%)	2/ 27 (7.4%)	0/ 55 (0%)	1/ 57 (1.8%)
Pulmonary Haemorrhage	2/ 22 (9.1%)	1/ 28 (3.6%)	4/ 57 (7.0%)	3/ 54 (5.6%)	3/ 34 (8.8%)	1/ 27 (3.7%)	3/ 55 (5.5%)	7/ 57 (12.3%)
Pulmonary Hypertension	2/ 22 (9.1%)	1/ 28 (3.6%)	2/ 57 (3.5%)	6/ 54 (11.1%)	5/ 34 (14.7%)	3/ 27 (11.1%)	3/ 55 (5.5%)	5/ 57 (8.8%)
Necrotizing Colitis	0/ 22 (0%)	0/ 28 (0%)	0/ 57 (0%)	0/ 54 (0%)	0/ 34 (0%)	0/ 27 (0%)	0/ 55 (0%)	0/ 57 (0%)
Patent Ductus Arteriosus Ligation	0/ 22 (0%)	0/ 28 (0%)	1/ 57 (1.8%)	0/ 54 (0%)	0/ 34 (0%)	1/ 27 (3.7%)	0/ 55 (0%)	2/ 57 (3.5%)
Gastrointestinal Perforation	0/ 22 (0%)	2/ 28 (7.1%)	0/ 57 (0%)	2/ 54 (3.7%)	1/ 34 (2.9%)	2/ 27 (7.4%)	1/ 55 (1.8%)	3/ 57 (5.3%)
Severe Intraventricular Haemorrhage before 40 weeks PMA	4/ 22 (18.2%)	7/ 28 (25.0%)	4/ 57 (7.0%)	4/ 54 (7.4%)	5/ 34 (14.7%)	6/ 27 (22.2%)	5/ 55 (9.1%)	3/ 57 (5.3%)
Periventricular Leukomalacia	0/ 22 (0%)	0/ 28 (0%)	1/ 57 (1.8%)	0/ 54 (0%)	0/ 34 (0%)	1/ 27 (3.7%)	0/ 55 (0%)	0/ 57 (0%)
Late-Onset Sepsis or Systemic Candida Infection	7/ 22 (31.8%)	7/ 28 (25.0%)	8/ 57 (14.0%)	5/ 54 (9.3%)	5/ 34 (14.7%)	9/ 27 (33.3%)	7/ 55 (12.7%)	9/ 57 (15.8%)
Late-Onset Systemic Candida Infection	1/ 22 (4.5%)	3/ 28 (10.7%)	0/ 57 (0%)	0/ 54 (0%)	1/ 34 (2.9%)	1/ 27 (3.7%)	0/ 55 (0%)	1/ 57 (1.8%)
Insulin Requirement During First Two Weeks of Life	12/ 22 (54.5%)	17/ 28 (60.7%)	22/ 57 (38.6%)	17/ 54 (31.5%)	16/ 34 (47.1%)	17/ 27 (63.0%)	18/ 55 (32.7%)	14/ 57 (24.6%)
Cerebral White Matter Lesions	0/ 22 (0%)	0/ 28 (0%)	0/ 57 (0%)	0/ 54 (0%)	0/ 34 (0%)	0/ 27 (0%)	0/ 55 (0%)	0/ 57 (0%)
Haemodynamic Failure	0/ 22 (0%)	0/ 28 (0%)	0/ 57 (0%)	0/ 54 (0%)	1/ 34 (2.9%)	0/ 27 (0%)	0/ 55 (0%)	0/ 57 (0%)

N = Number of patients with non-missing cortisol value at baseline within the group.
n = Number of patients with non-missing cortisol value at baseline within the category
n' = Number of patients with non-missing cortisol value at baseline within the group.
Percentages are calculated with respect to the number of patients within the group.
AESI = Adverse Event of Special Interest, HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-Menstrual Age.
The baseline cortisol median values for patients in stratum 1 (<26.0 Wks PMA) and stratum 2 (>=26.0 Wks PMA) are 433 and 462 respectively.
Reference listing: 16.2.7.3.a

Table 26: (same as table 36 in the Add CSR) Summary of AESIs Off-Treatment (D11 to W36 of PMA) by Baseline Cortisol Level for Patients with Non-Missing Baseline Cortisol Level

Variable	HCHS				Placebo			
	<26.0 Wks PMA n/n' (%)		>=26.0 Wks PMA n/n' (%)		<26.0 Wks PMA n/n' (%)		>=26.0 Wks PMA n/n' (%)	
	Cortisol <= Median (N = 22)	Cortisol > Median (N = 28)	Cortisol <= Median (N = 57)	Cortisol > Median (N = 54)	Cortisol <= Median (N = 34)	Cortisol > Median (N = 27)	Cortisol <= Median (N = 55)	Cortisol > Median (N = 57)
Any Early Respiratory Complication	0/ 22 (0%)	0/ 28 (0%)	0/ 57 (0%)	0/ 54 (0%)	0/ 34 (0%)	0/ 27 (0%)	0/ 55 (0%)	0/ 57 (0%)
Air Leaks	0/ 22 (0%)	0/ 28 (0%)	1/ 57 (1.8%)	0/ 54 (0%)	1/ 34 (2.9%)	1/ 27 (3.7%)	0/ 55 (0%)	1/ 57 (1.8%)
Pulmonary Haemorrhage	1/ 22 (4.5%)	0/ 28 (0%)	1/ 57 (1.8%)	0/ 54 (0%)	2/ 34 (5.9%)	0/ 27 (0%)	0/ 55 (0%)	1/ 57 (1.8%)
Pulmonary Hypertension	4/ 22 (18.2%)	0/ 28 (0%)	5/ 57 (8.8%)	2/ 54 (3.7%)	3/ 34 (8.8%)	3/ 27 (11.1%)	2/ 55 (3.6%)	1/ 57 (1.8%)
Necrotizing Colitis	0/ 22 (0%)	5/ 28 (17.9%)	5/ 57 (8.8%)	3/ 54 (5.6%)	1/ 34 (2.9%)	0/ 27 (0%)	3/ 55 (5.5%)	4/ 57 (7.0%)
Patent Ductus Arteriosus Ligation	3/ 22 (13.6%)	6/ 28 (21.4%)	5/ 57 (8.8%)	6/ 54 (11.1%)	14/ 34 (41.2%)	4/ 27 (14.8%)	5/ 55 (9.1%)	7/ 57 (12.3%)
Gastrointestinal Perforation	0/ 22 (0%)	1/ 28 (3.6%)	0/ 57 (0%)	3/ 54 (5.6%)	1/ 34 (2.9%)	2/ 27 (7.4%)	0/ 55 (0%)	0/ 57 (0%)
Severe Intraventricular Haemorrhage before 40 weeks PMA	1/ 22 (4.5%)	2/ 28 (7.1%)	1/ 57 (1.8%)	3/ 54 (5.6%)	2/ 34 (5.9%)	2/ 27 (7.4%)	1/ 55 (1.8%)	0/ 57 (0%)
Periventricular Leukomalacia	0/ 22 (0%)	0/ 28 (0%)	1/ 57 (1.8%)	2/ 54 (3.7%)	5/ 34 (14.7%)	0/ 27 (0%)	2/ 55 (3.6%)	0/ 57 (0%)
Late-Onset Sepsis or Systemic Candida Infection	8/ 22 (36.4%)	15/ 28 (53.6%)	24/ 57 (42.1%)	27/ 54 (50.0%)	17/ 34 (50.0%)	9/ 27 (33.3%)	19/ 55 (34.5%)	19/ 57 (33.3%)
Late-Onset Systemic Candida Infection	0/ 22 (0%)	0/ 28 (0%)	0/ 57 (0%)	1/ 54 (1.9%)	0/ 34 (0%)	1/ 27 (3.7%)	0/ 55 (0%)	1/ 57 (1.8%)
Insulin Requirement During First Two Weeks of Life	0/ 22 (0%)	2/ 28 (7.1%)	1/ 57 (1.8%)	3/ 54 (5.6%)	1/ 34 (2.9%)	1/ 27 (3.7%)	2/ 55 (3.6%)	0/ 57 (0%)
Cerebral White Matter Lesions	0/ 22 (0%)	0/ 28 (0%)	0/ 57 (0%)	0/ 54 (0%)	0/ 34 (0%)	0/ 27 (0%)	0/ 55 (0%)	0/ 57 (0%)
Haemodynamic Failure	1/ 22 (4.5%)	0/ 28 (0%)	0/ 57 (0%)	0/ 54 (0%)	0/ 34 (0%)	0/ 27 (0%)	1/ 55 (1.8%)	0/ 57 (0%)

N = Number of patients with non-missing cortisol value at baseline within the group.
n = Number of patients with non-missing cortisol value at baseline within the category
n' = Number of patients with non-missing cortisol value at baseline within the group.
Percentages are calculated with respect to the number of patients within the group.
AESI = Adverse Event of Special Interest, HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-Menstrual Age.
The baseline cortisol median values for patients in stratum 1 (<26.0 Wks PMA) and stratum 2 (>=26.0 Wks PMA) are 433 and 462 respectively.
Reference listing: 16.2.7.3.b

- **LITERATURE DATA (AESI)**

Post-PREMILOC publication

Renolleau (2021)

High cortisol levels at baseline (just after birth) were associated with a greater risk of severe intraventricular hemorrhage and spontaneous intestinal perforation in infants treated with hydrocortisone and, therefore, a lower benefit/risk ratio for the treatment.

Table V. Multivariate logistic regression model for the association between cortisol serum concentration (z score, 1 SD) and specific adverse neonatal outcomes in infants treated by early hydrocortisone or placebo

	Hydrocortisone (n = 145)		Placebo (n = 163)	
SAEs	aOR [95% CI]*	*P* value	aOR [95% CI]*	*P* value
Grade 3-4 IVH	1.82 [1.06; 3.15]	.03	0.86 [0.47; 1.55]	.61
Spontaneous intestinal perforation	4.81 [1.34; 17.22]	.02	1.35 [0.57; 3.21]	.50
Severe late-onset sepsis	1.06 [0.72; 1.55]	.78	1.07 [0.71; 1.61]	.74

*Adjusted for multiple gestation, antenatal steroids, early onset sepsis, peridural analgesia, and gestational hypertension.

Trials using the PREMILOC dosing regime

Briscoe et al (2022)

This single-centre retrospective cohort study of infants born <28 weeks' gestation assessed the safety of the routine use of low-dose prophylactic HC (N=103) in comparison with pre-HC implementation (N=88) [Briscoe 2022]. HC was administered as 1 mg/kg/day for 7 days, followed by 0.5 mg/kg/day for 3 days, starting during the first 24 hours of life. In comparison to the pre-HC group, the incidence

of spontaneous intestinal perforation in the HC group was 7.7 % (vs 3.4 % p = 0.2), necrotizing enterocolitis 30 % (vs 25 % p = 0.43) and late onset sepsis 34 % (vs 30.6 % p = 0.63). In conclusion, in this study on 72 subjects, prophylactic administration of low-dose HC for BPD to infants <28 WA was not associated with an increase in serious adverse outcomes.

Table 27: Adverse events in the pre-hydrocortisone and the hydrocortisone groups

	Pre-hydrocortisone N = 88 (%)	Hydrocortisone N = 103 (%)	Pearson Chi-square (p)
NEC	22 (25 %)	31 (30 %)	0.43
SIP	3 (3.4 %)	8 (7.7 %)	0.2
LOS	27 (30.6 %)	35 (34 %)	0.63
23–25/40	21 (47.7 %)	21 (40.4 %)	0.47
26–28/40	6 (13.6 %)	14 (27.5 %)	0.1
Pneumothorax	4 (4.5 %)	6 (6 %)	0.69
Pulmonary haemorrhage	12 (13.6 %)	14 (13.6 %)	0.99
Insulin	33 (37.5 %)	46 (44.7 %)	0.32
Severe IVH (3/4)	18 (20.4 %)	17 (16.5 %)	0.50
Cystic PVL	5 (5.6 %)	2 (1.9 %)	0.17
Severe ROP	8 (9 %)	5 (4.9 %)	0.28
Death pre-discharge	18 (20.4 %)	19 (18.4 %)	0.73

NEC: necrotising enterocolitis; SIP: spontaneous intestinal perforation; LOS: late onset sepsis; IVH: intraventricular haemorrhage; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity.

Shah et al (2024)

This single-center retrospective study compared risk-adjusted rates of survival without BPD, BPD, bowel perforation, and late-onset sepsis among infants (22–27 weeks' gestation at birth) who received HC (n=82) and who did not (n =205). HC was initiated within 24h of life using the following protocol: 0.5 mg/kg every 12 h for the first 7 days, followed by 0.5 mg/ kg once daily for 3 days.

Infants in the HC group were of lower gestational age, lower birthweight, and higher day-1 risk of death/BPD. Bowel perforation or sepsis rate were similar among both groups.

Table 28: Risk-adjusted outcomes

Table 3. Risk-adjusted outcomes.

Outcome	Treated with PEH (*n* = 82)	Not treated with PEH (*n* = 205)	Unadjusted odds ratio (confidence interval)	Adjusted odds ratio (confidence interval)[a]	*p*-value for adjusted odds ratio
Primary composite outcome – survival without BPD	36 (43.9%)	84 (40.5%)	1.2 (0.68–1.9)	**2.04 (1.1–3.7)**	**0.02**
Survived at 36 weeks' PMA	69 (84.1%)	182 (88.8%)	0.67 (0.32–1.4)	0.96 (0.44–2.1)	0.91
Grade 1–3 BPD	33/69 (47.8%)	98/182 (53.8%)	0.79 (0.45–1.4)	**0.46 (0.25–0.87)**	**0.02**
Composite safety outcome – death or bowel perforation or late-onset sepsis	39 (47.6%)	72 (35.1%)	1.7 (0.99–2.8)	1.3 (0.77–2.3)	0.31
Bowel Perforation	6/77 (7.8%)	18/195 (9.2%)	0.83 (0.32–2.2)	0.67 (0.25–21.8)	0.43
Late-Onset Sepsis	24/78 (30.8%)	47/197 (23.9%)	1.4 (0.79–2.5)	1.2 (0.65–2.2)	0.56

BPD bronchopulmonary dysplasia.
Bold values indicates statistical significance.
[a]Outcome was adjusted for risk for BPD or death.

Clinical outcomes		Treated with PEH ($n = 82$)	Not Treated with PEH ($n = 205$)	p-value
Respiratory outcomes				
Jensen BPD criteria	Grade 0	36/69 (52.2%)	84/182 (46.1%)	0.4
	Grade 1	15/69 (21.7%)	48/ 182 (26.4%)	0.52
	Grade 2	12/ 69 (17.4%)	30/182 (16.5%)	0.85
	Grade 3	6/69 (8.7%)	20/182 (11%)	0.82
	Grade 1–3	33/69 (47.8%)	98/182 (53.8%)	0.4
Other neonatal outcomes[a]				
Survived at 36 weeks' PMA		69/82 (84.1%)	182/205 (88.8%)	0.32
Days to reach full feeds		14 (12, 19)	14 (11, 19)	0.18
NEC ≥ stage 2		13/77 (16.7%)	50/195 (25.9%)	0.15
Surgical NEC or bowel perforation		6/77 (7.8%)	18/195 (9.2%)	0.82
Culture-positive sepsis, >48 h		24/78 (30.8%)	47/197 (23.9%)	0.28
PDA treatment		7/74 (9.5%)	54/189 (28.6%)	**<0.001**
PDA ligation		4/74 (5.4%)	10/189 (5.3%)	0.97
Severe IVH (grades 3–4)		14/79 (17.7%)	38/200 (19%)	0.87
Treatment for ROP		12/70 (16.9%)	25/179 (13.9%)	0.55
Survived at discharge		69/82 (84.1%)	178/204 (87.2%)	0.57
Length of stay (days)[b]		97 (72, 129)	85.5 (68, 109)	0.08
PMA at discharge (weeks)[b]		38 (37, 43)	38 (36, 41)	0.35
Weight at 36 weeks' PMA (grams)[b]		2180 (2010, 2336)	2195.5 (2000, 2414)	0.37
Weight at discharge (grams)[b]		2895 (2408, 3545)	2697 (2300, 3370)	0.16
Discharge head circumference (cm)[b]		33 (32, 35)	32 (31, 34)	0.10
Discharge length (cm)[b]		47 (45, 50)	46 (44, 49.5)	0.34
Gastrostomy tube placement		7/69 (10.1%)	18/178 (10.1%)	1
Respiratory support at discharge	Any oxygen support at discharge	28/69 (40.1%)	71/177 (40.1%)	0.89
	Tracheostomy	3/69 (4.3%)	10/177 (5.6%)	0.91

PEH prophylactic early low-dose hydrocortisone, *BPD* bronchopulmonary dysplasia (no BPD if with no respiratory support, grade 1 with ≤2 L/min nasal cannula (NC), grade 2 with >2 L/min NC or non-invasive positive airway pressure, or grade 3 with invasive mechanical ventilation at 36 weeks' postmenstrual age), *IVH*

Studies with dosing schemes similar to PREMILOC

Bonsante 2007

In this study performed in 50 infants who received either HC 0.5 mg/kg/12 h for 9 days, then HC 0.5 mg/kg/24 h for 3 days or a placebo, hypotension after recruitment was reduced by HC (0 vs.30%). There were 2 gastrointestinal perforations in the HC group vs 1 in the placebo group, all in subjects who received a concomitant treatment with ibuprofen. The incidence of other adverse effects was similar between the two groups.

	HC treatment (n = 25)	Placebo (n = 25)	p
NEC	1/24 (4.1%)	2/21 (9.4%)	NS
GI perforation	2/24 (8.3%)	1/21 (4.7%)	NS
NEC related	1/24 (4.1%)	1/24 (4.1%)	NS
Spontaneous	1/24 (4.1%)	0/21 (0.0%)	NS
Hypertension	3/21 (14%)	1/21 (4.7%)	NS
Hyperglycemia	11/25 (44%)	12/22 (54%)	NS
Hyperkalemia	6/25 (24%)	2/22 (9.0%)	NS
Sepsis	6/25 (24%)	4/22 (18%)	NS
Fungal infection	3/25 (12%)	3/22 (13%)	NS

Watterberg 2004

In this prospective, placebo-controlled, double-blind study, 360 infants weighing 500-999g. received either HC or a placebo. HC was started between 12 and 48h, 1 mg/kg per day for 12 days, then 0.5 mg/kg per day for 3 days.

There were no differences between groups for the rates of hypo/hypernatremia; hyperkaliemia, hyperglycaemia, hypertension.

Patient enrolment was stopped at 360 patients because of an increase in spontaneous gastrointestinal perforation in the hydrocortisone-treated group. 12% HC subjects vs 6% placebo subjects, HC treated infants who received indomethacin were more likely to experience apparently spontaneous gastrointestinal perforation than placebo-treated infants who received indomethacin ($p< 0.001$, suggesting an interactive effect. The incidence of perforation in HC-treated infants who did not receive indomethacin was similar to that of the placebo group.

The combination of indomethacin and hydrocortisone should be avoided.

Outcome	Hydrocortisone	Placebo	Adjusted OR* (95% CI) or *P* Value	Unadjusted OR or *P* Value
Nosocomial infection, total babies	80/180 (44%)	75/180 (42%)	1.08 (0.70–1.68)	1.12 (0.74–1.70)
Bacterial	73/180 (41%)	67/180 (37%)	1.12 (0.72–1.75)	1.15 (0.75–1.76)
Fungal	16/180 (9%)	20/180 (11%)	0.78 (0.37–1.65)	0.78 (0.39–1.56)
Intracranial hemorrhage				
All grades	73/172 (42%)	63/176 (36%)	1.33 (0.83–2.14)	1.32 (0.86–2.04)
Grade III/IV	33/172 (19%)	29/176 (16%)	1.25 (0.68–2.30)	1.20 (0.69–2.09)
Periventricular leukomalacia (central reader)	8/112 (7%)	9/119 (8%)	0.98 (0.33–2.94)	0.94 (0.35–2.53)
Retinopathy of prematurity				
Any stage	122/153 (80%)	128/150 (85%)	0.64 (0.31–1.33)	0.68 (0.37–1.23)
≥Grade III	41/153 (27%)	47/150 (31%)	0.64 (0.35–1.16)	0.80 (0.49–1.32)
Intervention performed	18/153 (12%)	21/150 (14%)	0.65 (0.30–1.39)	0.82 (0.42–1.61)
NEC	7/180 (4%)	14/180 (8%)	0.47 (0.18–1.22)	0.48 (0.19–1.22)
Gastrointestinal perforation				
Spontaneous or NEC-related§	22/180 (12%)	11/180 (6%)	1.98 (0.91–4.33)	2.14 (1.01–4.55)
Likely NEC	5/180 (3%)	7/180 (4%)	0.66 (0.19–2.29)	0.71 (0.22–2.27)‡
Likely spontaneous	17/180 (9%)	4/180 (2%)	4.67 (1.43–15.30)‡ (*P* = .01)‡	4.59 (1.51–13.92) (*P* = .01)

* ORs are adjusted for center, birth weight, and risk factors.
† Of the survivors.
‡ Significantly different between groups.
§ Not including 2 unrelated (ileal atresia and intussusception).

Reviews and meta-analyses illustrating short term safety with early administration of HC

Morris et al 2019

This review and meta-analysis included 12 studies with early use of HC for BPD prevention (5 studies) or another indication.

Gastrointestinal perforation was significantly higher in the group of infants receiving HC (all studies: RR 1.69 [1.07, 2.68], p = 0.03, number needed to harm (NNH) 30 [15.9, 193.9]; BPD-studies: RR 1.76 [1.09, 2.84], p = 0.02, NNH 28 [15.0, 159.2]).

Early treatment with HC significantly reduced the risk of treatment for PDA (all-studies: 0.66 [0.52, 0.84], p < 0.01, NNT 11 [6.8, 25.9], BPD- studies: 0.66 [0.49, 0.88], p < 0.01, NNT 11 [6.3, 37.6]).

Outcome	Hydrocortisone		Control		Number of trials	Risk ratio (95% CI) OR SMD (95% CI)	*p* value	NNT/H (95% CI)
	Events	Total	Events	Total				
BPD studies								
Survival to discharge	417	505	401	515	5	1.06 (1.00, 1.13)	0.06	
Sepsis	179	505	155	514	5	1.17 (0.99, 1.40)	0.07	
Pulmonary air leak	30	460	29	471	3	1.04 (0.64, 1.70)	0.86	
Pulmonary haemorrhage	37	435	30	446	2	1.26 (0.79, 2.01)	0.33	
GI bleeding	2	25	1	26	1	2.08 (0.20, 21.52)	0.54	
Treated for hyperglycaemia	196	460	184	472	3	1.09 (0.94, 1.28)	0.25	
Treated for hypertension	4	180	5	180	1	0.80 (0.22, 2.93)	0.74	
Any IVH	93	217	82	222	3	1.16 (0.92, 1.46)	0.20	
IVH grade III–IV	77	497	74	509	5	1.07 (0.80, 1.44)	0.65	
PVL	16	415	23	431	4	0.72 (0.39, 1.34)	0.30	
NEC	29	504	31	513	5	0.95 (0.58, 1.55)	0..84	
Discharged with home oxygen (survivors)	18	246	24	238	3	0.74 (0.42, 1.28)	0.28	
Duration of mechanical ventilation (days)		249		249	4	− 2.69 (− 6.98, 1.59)	0.22	
Duration of stay (days)		222		221	4	− 1.02 (− 6.35, 4.31)	0.71	
Treated for PDA[d]	54	300	85	312	3	0.66 (0.49, 0.88)	< 0.01	11 (6, 3, 37.6)
Treated for ROP	24	453	28	462	4	0.85 (0.51, 1.42)	0.54	

[a] Only first episode of sepsis included from Biswas 2003

[b] Bourchier (1997) and Efird (2005) reported IVH grades II–IV

[c] Efird (2005) reported duration of stay in survivors only

Shaffer et al 2019

This individual Patient Data Meta-Analysis included 4 randomised controlled trials (N=982).

The therapy was associated with an increased risk of spontaneous gastrointestinal perforation (OR, 2.50; 95% CI, 1.33-4.69; p = 0.004; I2 = 31.9%) when HC was given in association with indomethacin exposure. The incidence of late-onset sepsis was increased in infants exposed to HC (OR, 1.34; 95% CI, 1.02-1.75; P = .04; I2 = 0%), but no adverse effects were reported for either death or 2-year neurodevelopmental outcomes as assessed in an aggregate meta-analysis.

Table 29: Results of individual patient data meta-analysis of all outcomes adjusted for sex, gestational age, and any antenatal steroids

Outcomes	Hydrocortisone	Placebo	OR or Mean Difference	95% CI of OR or Mean Difference	*P* Value
Survival without BPD at 36 wk PMA, n/N (%)	258/484 (53.3)	225/495 (45.5)	1.45	1.11-1.90	.007
Death before 36 wk PMA, n/N (%)	79/484 (16.3)	98/495 (19.8)	0.76	0.54-1.07	.12
BPD at 36 wk PMA, n/N (%)	147/405 (36.3)	172/397 (43.3)	0.73	0.54-0.98	.038
Death before discharge, n/N (%)	85/485 (17.5)	112/497 (22.5)	0.70	0.51-0.97	.0327
Weight at 36 wk PMA, g, mean	2036 (n = 390)	2061 (n = 379)	−24.11	−71.36 to 23.14	.32
Head circumference at 36 wk, cm, mean	31.0 (n = 346)	30.9 (n = 337)	0.19	−0.05 to 0.42	.12
Respiratory support					
Days of ventilation, mean	32.3 (n = 226)	31.7 (n = 221)	−0.63	−7.28 to 6.01	.85
Days of CPAP, mean	17.2 (n = 47)	17.7 (n = 49)	−0.12	−5.78 to 5.55	.97
Days of oxygen, mean	74.1 (n = 226)	75.2 (n = 221)	−2.17	−12.07 to 7.73	.67
Oxygen at discharge, n/N (%)	73/401 (18.2)	75/386 (19.4)	0.92	0.64-1.33	.65
Open-label steroid use, n/N (%)	195/485 (40.2)	211/497 (42.5)	0.90	0.70-1.17	.44
Pneumothorax, n/N (%)	31/485 (6.39)	32/497 (6.44)	0.98	0.58-1.64	.93
Insulin treatment, n/N (%)	204/485 (42.1)	194/497 (39.0)	1.12	0.86-1.45	.42
Medical treatment for PDA (indomethacin or ibuprofen), n/N (%)	202/485 (41.7)	246/497 (49.5)	0.72	0.56-0.93	.012
Any prophylactic indomethacin, n/N (%)	61/485 (12.6)	63/497 (12.7)	0.96	0.65-1.41	.83
Surgical ligation, n/N (%)	68/485 (14.0)	83/497 (16.7)	0.80	0.56-1.14	.21
Necrotizing enterocolitis, n/N (%)	27/485 (5.57)	29/497 (5.84)	0.95	0.55-1.63	.85
Spontaneous gastrointestinal perforation	35/483 (7.25)	15/497 (3.02)	2.50	1.33-4.69	.004
Late-onset sepsis (bacterial/fungal), n/N (%)	176/485 (36.3)	148/497 (29.8)	1.34	1.02-1.75	.0357
Severe IVH (grade 3-4), n/N (%)	76/477 (15.9)	71/493 (14.4)	1.10	0.76-1.59	.60
Cystic PVL, n/N (%)	22/447 (4.92)	25/459 (5.45)	0.89	0.49-1.60	.69
Severe ROP, n/N (%)	50/458 (10.9)	54/467 (11.6)	0.92	0.59-1.45	.72

Adverse events reported during the long-term study (PREMILOC, FUS population)

In this population (i.e., subjects followed up to 2 years) of subjects, at least one TEAE was reported for 87.8% of HC subjects and for 94.1% of placebo subjects, and at least one TEAE occurring after 36 weeks of PMA was reported for 12.2% of HC subjects vs 7.4% of placebo subjects (Table 30).

Table 30: TEAEs with onset after 36 weeks (FUS)

MedDRA (V18.0) System Organ Class Preferred Term	HCHS (N = 197) n (%) nae	Placebo (N = 188) n (%) nae
Any TEAE with onset after 36 weeks	24 (12.2%) 68	14 (7.4%) 20
Gastrointestinal disorders	5 (2.5%) 6	6 (3.2%) 8
Infections and infestations	9 (4.6%) 14	1 (0.5%) 1
Eye disorders	6 (3.0%) 8	3 (1.6%) 4
Respiratory, thoracic and mediastinal disorders	5 (2.5%) 9	1 (0.5%) 1
Surgical and medical procedures	3 (1.5%) 3	2 (1.1%) 2
General disorders and administration site conditions	4 (2.0%) 5	0 (0%) 0
Congenital, familial and genetic disorders	1 (0.5%) 1	2 (1.1%) 2
Investigations	3 (1.5%) 8	0 (0%) 0
Metabolism and nutrition disorders	3 (1.5%) 4	0 (0%) 0
Nervous system disorders	1 (0.5%) 4	1 (0.5%) 2
Blood and lymphatic system disorders	1 (0.5%) 1	0 (0%) 0
Cardiac disorders	1 (0.5%) 2	0 (0%) 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5%) 2	0 (0%) 0
Reproductive system and breast disorders	1 (0.5%) 1	0 (0%) 0

N = Number of subjects within the group, n = Number of subjects within the category, nae = Number of adverse events; TEAE = Treatment-Emergent Adverse Event, HCHS = Hydrocortisone Hemisuccinate; Ordering of MedDRA System Organ Class is based on descending frequency of subjects with events in the total population

Deaths

A total of 48 HC subjects and 66 placebo subjects with TEAE leading to death were described in the study report. An additional placebo subject is not present in this listing but present in the narratives. The date of occurrence of this AE leading to death (gastrointestinal perforation and septic shock) in the database is not valid with an AE supposed to occur before birth and therefore not included in the listing of TEAEs. one HC subject is not included in the narratives as, although randomised, he did not receive the study treatment.

3.3.9.6. Laboratory findings

A full *post-hoc* analysis of laboratory parameters was initially planned. However, only glycaemia was available, and data presented at each assessment time see Figure below.

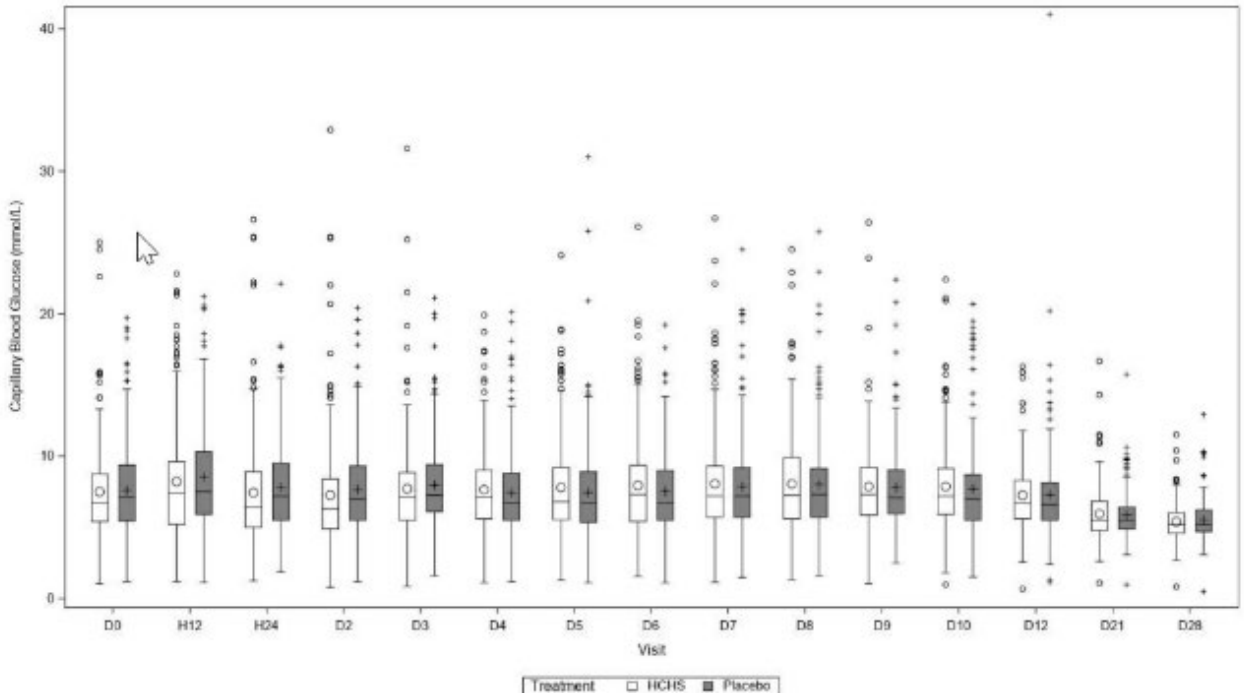


Figure 3: Capillary blood glucose at each assessment time (SAF)

No major differences between the two treatment groups are noted throughout the study. However, overall, the < 26 weeks PMA population has a higher median capillary blood sugar already at baseline and then throughout the measurement period compared to the ≥26 weeks PMA population (HC baseline value: 7.5 vs 6.45 mmol/L; HC D10 value: 7.60 vs 6.95 mmol/L). This applies to both treatment groups.

3.3.9.7. In vitro biomarker test for patient selection for safety

Not applicable.

3.3.9.8. Safety in special populations

Table 31: An AE summary for the on/off treatment group by PMA age at birth

AE summary for the on/off treatment group by PMA age at birth				
	HCHS N=253		**Placebo N=264**	
MedDRA Terms	Gestational age <26 wks (n=82) n (%)	Gestational age ≥26 wks (n=171) n (%)	Gestational age <26 wks (n=90) n (%)	Gestational age ≥26 wks (n=174) n (%)
D1-D10				
Total AEs	76 (92.7%)	121 (70.8%)	85 (94.4%)	144 (82.8%)
Serious AEs – Total	61 (74.4%)	86 (50.3%)	67 (74.4%)	85 (48.9%)
- Fatal	20 (24.4%)	8 (4.7%)	15 (16.7%	15 (8.6%)
- Life-threatening	NA	NA	NA	NA
- Disability/incapacity	NA	NA	NA	NA
- Other (medically significant)	NA	NA	NA	NA
AE leading to dose reduction//interruption	0	0	0	0
Infections and infestations	30 (36.6%)	32 (18.7%)	25 (27.8%)	39 (22.4%)
- Sepsis neonatal	24 (29.3%)	28 (16.4%)	19 (21.1%)	34 (19.5%)
- Sepsis	4 (4.9%)	4 (2.3%)	1 (1.1%)	3 (1.7%)
Metabolism and nutrition disorder	44 (53.7%)	63 (36.8%)	53 (58.9%)	5 (32.2%)
- Hyperglycaemia/ Insulin requirement during first two weeks of life	44 (53.7%)	63 (36.8%)	53 (58.9%)	56 (32.2%)
Gastrointestinal disorders	5 (6.1%)	8 (4.7%)	5 (5.6%)	4 (2.3%)
- GI perforations	4 (4.9%)	4 (2.3%)	4 (4.4%)	4 (2.3%)
- NEC	1 (1.2%)	1 (0.6%)	0 (0%)	0 (0%)
Intra ventricular haemorrhages				
- all	29 (35.4%)	32 (18.7%)	34 (37.8%)	36 (20.7%)
- severe (SAE or grade >2)	17 (20.7%°	10 (5.8%)	19 (21.1%)	14 (8.0%)
D11-W36 of PMA				
Total AEs	62 (75.6%)	114 (66.7%)	71 (78.9%)	109 (62.6%)
Serious AEs – Total	52 (63.4%)	69 (40.4%)	57 (63.3%)	74 (42.5%)
- Fatal	19 (23.2%)	10 (5.8%)	26 (28.9%)	10 (5.7%)
- Life-threatening	NA	NA	NA	NA
- Disability/incapacity	NA	NA	NA	NA
- Other (medically significant)	NA	NA	NA	NA
AE leading to dose reduction//interruption	0	0	0	0
Infections and infestations	36 (43.9%)	81 (47.4%)	38 (42.2%)	59 (33.9%)
- Sepsis neonatal	30 (36.6%)	67 (39.2%)	31 (34.4%)	57 (32.8%)
- Sepsis	4 (4.9%)	11 (6.4%)	3 (3.3%)	9 (5.2%)
Metabolism and nutrition disorder	7 (8.5%)	8 (4.7%)	6 (6.7%)	10 (5.7%)
- Hyperglycaemia/Insulin requirement during first two weeks of life	3 (3.7%)	4 (2.3%)	4 (4.4%)	4 (2.3%)
Gastrointestinal disorders	13 (15.9%)	18 (10.5%)	6 (6.7%)	15 (8.6%)
- GI perforations	3 (3.7%)	4 (2.3%)	4 (4.4%)	0
- NEC	7 (8.5%)	10 (5.8%)	1 (1.1%)	10 (5.7%)
Intra ventricular haemorrhages				

AE summary for the on/off treatment group by PMA age at birth				
	HCHS N=253		**Placebo N=264**	
MedDRA Terms	Gestational age <26 wks (n=82) n (%)	Gestational age ≥26 wks (n=171) n (%)	Gestational age <26 wks (n=90) n (%)	Gestational age ≥26 wks (n=174) n (%)
- all	15 (18.3%)	23 (13.5%)	12 (13.3%)	13 (7.5%)
- severe (SAE or grade >2)	8 (9.8%)	8 (4.7%)	9 (10.0%)	3 (1.7%)

3.3.9.9. Immunological events

No immunological events were reported by the applicant.

3.3.9.10. Safety related to drug-drug interactions and other interactions

The interactions proposed in SmPC section 4.5 for the product are based on interactions considered relevant for the intended population and labelled in the SmPC section for Hydrocortisone containing medicinal products. This approach is considered acceptable. However, some editorial changes are proposed. See annotated SmPC.

3.3.9.11. Discontinuation due to adverse events

Reasons for discontinuation due to adverse events by period is presented in the table below.

Table 32: Reason for Discontinuation by Period

	HCHS			Placebo		
	<26.0 Wks PMA (N = 83) n/N (%)	>=26.0 Wks PMA (N = 172) n/N (%)	All Patients (N = 255) n/N (%)	<26.0 Wks PMA (N = 90) n/N (%)	>=26.0 Wks PMA (N = 174) n/N (%)	All Patients (N = 264) n/N (%)
On-treatment (D1 - D10)						
Serious Adverse Event Leading to Death	10/ 83 (12.0%)	3/172 (1.7%)	13/255 (5.1%)	7/ 90 (7.8%)	10/174 (5.7%)	17/264 (6.4%)
Other	0/ 83 (0%)	0/172 (0%)	0/255 (0%)	0/ 90 (0%)	0/174 (0%)	0/264 (0%)
Off-treatment (D11 to 36 Weeks of PMA)						
Serious Adverse Event Leading to Death	24/ 83 (28.9%)	10/172 (5.8%)	34/255 (13.3%)	31/ 90 (34.4%)	12/174 (6.9%)	43/264 (16.3%)
Other	0/ 83 (0%)	0/172 (0%)	0/255 (0%)	0/ 90 (0%)	0/174 (0%)	0/264 (0%)
Long-Term Follow-Up (36 Weeks of PMA to 2 Years)						
Serious Adverse Event Leading to Death	1/ 83 (1.2%)	0/172 (0%)	1/255 (0.4%)	2/ 90 (2.2%)	5/174 (2.9%)	7/264 (2.7%)
Other	0/ 83 (0%)	7/172 (4.1%)	7/255 (2.7%)	0/ 90 (0%)	6/174 (3.4%)	6/264 (2.3%)

N = Number of patients within the group, n = Number of patients within the category.
Percentages are calculated with respect to the number of patients within the group.
HCHS = Hydrocortisone Hemisuccinate, Wks = Weeks, PMA = Post-Menstrual Age.

3.3.9.12. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country for the prevention of BPD.

3.3.10. Discussion on clinical safety

The safety data presented is based both on the PREMILOC study and on data from publications reporting the use of HC in premature children for any indication, i.e., mainly respiratory indication or hemodynamic failure.

Exposure

In the pivotal trial (PREMILOC), 253 premature children (n=82 < 26 weeks [32%] and n=171 ≥ 26 weeks [68%]) were exposed to HC. In addition, in three published clinical trials (Briscoe et al, Dubner et al, and Shah et al) a total of 218 premature infants were exposed to HC with the same dosing scheme as used in the PREMILOC study for prevention of BPD. Another 450 neonates have been exposed with HC doses similar to the PREMILOC dosing scheme (Watterberg et al 1999, Watterberg et al 2004 and Bonsante 2007). Safety data up to 2 years is available in 197/253 in the HC group and 188/264 in the placebo group. The safety database is considered sufficient in size, and the length of follow-up sufficient given the intended use of the product.

Adverse events

The primary evaluation (i.e., whole study) period for safety/adverse events is the time from start of study treatment (D1) up to 36 weeks PMA. Thus, the AE follow-up time includes both data from the on-**treatment period (D1-Day10)** as well as an **off-treatment period form D11 to 36 weeks PMA**.

AEs (inclusively SAEs and fatal events) are, in both treatment groups, reported more frequently in infants born < 26 weeks PMA compared to those born > 26 weeks PMA.

During the whole study period, any adverse events were reported by 89.7% in the HC group and 95.8% in the placebo group. The most reported PTs were "neonatal sepsis" (51% vs 47.3%), "patent ductus arteriosus" (51.0% vs 60.6%), "hyperglycaemia" (44.7% vs 43.6%) and "intraventricular haemorrhage" (35.6% vs 33.0%). Any SAEs were reported by approximately 75% of the participants in both treatment groups. Higher frequencies of SAEs were noted in the <26 weeks populations (~90%). The most reported SAEs during the whole study were "hyperglycaemia" (HCHS: 32.0% vs placebo: 30.7%), "patent ductus arteriosus" (HC: 15.8% vs placebo: 22%), and "intraventricular haemorrhage" (HCHS: 15.0% vs placebo: 15.2%). A difference in frequency between the two treatment groups are noted for SAEs in the SOCs "Infections and infestations" (33.6% vs 25.0%, driven by PTs related to sepsis) and "Gastrointestinal disorders" (12.3% vs 9.5% driven by PTs necrotizing enterocolitis (NEC) and gastrointestinal perforation).

During the **on-treatment (D1-10)** period, PTs within the SOC Infections and infestations (driven by events related to **sepsis**) are more commonly reported for the HCHS treated infants born < 26 wks compared to the corresponding placebo group (SOC Infections; 36.6% vs 27.8%; neonatal sepsis: 29.3 vs 21.1% and sepsis: 4.9% vs 1.1%).

During the **off-treatment period (D11 to w36 PMA)**, sepsis (i.e., neonatal sepsis and septic shock), IVH, NEC and GI perforation are more commonly reported for all ages HCHS group compared to placebo (>2% difference). The difference between treatment groups was especially pronounced for the PT NEC in infants born < 26 wks PMA (HCHS 8.5% vs 1.1.% in the placebo group) and for all birth PMA ages for the PT gastrointestinal perforations (HCHS: 2.4% vs 0.4% with placebo) and the PT IVH (HCHS: 15.0% vs 9.5% with placebo).

Deaths/fatal events

In the initial submission, it was informed that up to week 36 PMA, deaths were reported in 47 cases (18.6%) in the HC group and 66 cases (25%) in the placebo group. However, with the response the Applicant informs that any **fatal SAE** was reported by 28 infants in the HCHS group on-treatment and 29 off treatment, thus it appears that in total 57 infants in the HCHS group and not 47 reported any fatal AEs. This difference should be clarified.

Based on new data presented with the response, overall similar proportions of fatal event were reported in the two treatment groups both during on-treatment (~11% in both groups) and off-

treatment (~11% in the HCHS group and 13% with placebo). In both treatment groups, fatal events were, as expected, more common in infants born < 26 weeks PMA. However, in this population fatal events were more commonly reported in the HCHS group (24.4%) compared to placebo (16.7%) during the on-treatment period (D1-D10). The main reason for fatal events in the HCHS group were IVH. In the HCHS treated < 26 wks PMA infants, fatal IVH events were reported by 12.2% compared to 4.4% in the corresponding placebo group.

Adverse events of special interest (AESI)

Gastrointestinal perforation (GI) is a known risk when HC is used in combination with NSAID (Morris et al [2019], Shaffer et al [2019], Doyle 2021 et al and Ramaswamy 2021 et al). Concomitant use of NSAID was not allowed in the PREMILOC trial.

During the **on-treatment period (D1-D10)**, GI perforations was reported only in slightly higher proportion of patients in the HCHS group compared to placebo (GI perforations: HCHS 3.2% vs 3.0% with placebo). In both treatment groups, GI perforations were more commonly reported in the <26.0 weeks PMA groups. However, during the **off-treatment period (D11 up to 36 wks PMA)**, GI perforations were reported in a larger proportion of patients in the HCHS group compared to placebo (GI perforation: 2.8% vs 1.5%). The risk for GI perforations is reflected in the SmPC sections 4.4, 4.5 and 4.8 and included as an important identified risk in the RMP.

Necrotising enterocolitis (NEC) was reported only in slightly higher proportion of patients in the HCHS group compared to placebo (0.8% vs 0%) during the **on-treatment period**. However, during the **off-treatment period**, the risk for NEC had increased and was larger for the infants treated with HCHS compared to placebo (6.7% vs 4.2%). The difference was especially pronounced in the infants born <26.0 weeks PMA group (HCHS: 8.5% vs placebo: 1.1%). During the off-treatment period, 18% of the children in the <26.0 wks PMA group with a cortisol value > median reported events of NEC compared to none in the group with values below median or in the corresponding placebo group. The risk for NEC is reflected in the SmPC sections 4.4 and 4.8 and included as an important identified risk in the RMP.

Sepsis: The increased risk for infections during systemic treatment with HC is well known due to the immunosuppressive effect. In the PREMILOC trial, a higher proportion of infants in the HC group compared to those in the placebo group reported events within the SOC infections and infestations (33.6% vs 25.0%) driven by events related to sepsis.

During the **on-treatment period**, this difference is reflected by more commonly reported events of sepsis and neonatal sepsis in infants born < 26 weeks treated with HCHS compared to placebo (see under adverse events above). During the **off-treatment period**, the difference in events related to sepsis were instead more commonly reported in the whole HCHS group compared to placebo e.g. neonatal sepsis (38.3% vs 33.0%) and septic shock (6.3% vs 3.8%). During the off-treatment, a higher proportion of infants with cortisol levels > median reports events within the SOC Infections and infestations in the HCHS group (57.1% [infants born < 26 wks PMA] and 55.6% [infants born >26 to 36 wks PMA]) compared to those with cortisol levels < median (36.4% [infants born < 26 wks PMA] and 47.4% [infants born >26 to 36 wks PMA]). This pattern is not noted in the placebo group. The risk for concurrent infection including sepsis is reflected in SmPC sections 4.4 and 4.8.

Intraventricular haemorrhage (IVH)**:** In the literature there is support for a difference however small in frequencies of all IVH (Watterberg et al 2004, Briscoe et al 2022 and Morris 2019). However, there are more conflicting results presented regarding the risk for severe IVH. Watterberg et al 2004 and Briscoe et al 2022 publish higher frequencies in HC treated children compared to placebo but Morris et al 2019 (metanalysis), Shaffer et al 2019 (metanalysis) and Shah et al 2024 publish similar frequencies between the two treatment groups for this risk. In PREMILOC, the PT IVH overall

(regardless of severity) were slightly more commonly reported in the HC treated group (35.6%) compared to the placebo group (33.0%) during the whole study. The difference between the two treatment groups was more markedly during the off-treatment period, (IVH as PT: 15.0% in HCHS group vs 9.5% with placebo). Results of the outcome of IVH events have not clearly been presented. This is of importance since IVH were the most common reported fatal event in the HC treatment group.

Hyperglycaemia/insulin requirement: As in the literature (Morris et al [2019], Shaffer et al [2019], Briscoe et al [2022] and Shah et al [2024]), approximately 40% of the subjects in PREMILOC reported a need of insulin treatment during the first two weeks after study treatment initiation. There is no difference between the two treatment groups in the overall population with regards to insulin requirements or events of hyperglycaemia during the on-or off-treatment period. Acidosis and metabolic acidosis were reported by 0.8% (n=2) each in both treatment groups. However, it appears that within the HCHS group a slightly higher proportion of the patients with cortisol levels > median required insulin compared to those with < median cortisol levels. The risk for hyperglycaemia is reflected in SmPC section 4.8.

Retinopathy: Dexametasone treatment in premature children has been associated with an increased risk for severe retinopathy of prematurity (ROP) (Doyle et al 2010). In PREMILOC, a higher frequency of the children in the HC group reported retinopathy after 2 years (14.4% in the follow-up-set [FUS]) than the placebo group (9.2% in the FUS). Most of these events had a grade 1 or 2 ROP (6.2% each) and none in the HC group had a grade 4 ROP. The risk of ROP is therefore proposed to be followed via routine PV.

Hypertrophic cardiomyopathy: The risk for hypertrophic cardiomyopathy has been reported as a short-term effect of both high-dose and low-dose dexamethasone in preterm infants (Paech et al; J Perninatol 2014). In PREMILOC, hypertrophic cardiomyopathy was reported by only one subject in the HC group and none in the placebo group. Furthermore, one subject in each treatment group reported the PT 'cardiac hypertrophy' (SOC cardiac disorders). Hypertrophic cardiomyopathy is proposed by the applicant to be reflected in the SmPC section 4.4 and 4.8. However, the risk should also be included as an important potential risk in the RMP**.**

Neurological development: In the literature, an increased risk for impaired neurodevelopmental outcomes has been suggested during use of dexamethasone (Doyle et al, 2010) and in relation to hydrocortisone doses (Taniguchi et al; 2023) in neonate children. However, based on the presented 2- and 5-years data in PREMILOC, there were no signs of an increased risk for abnormal neurodevelopment for the early low-dose HCHS treated children compared to the placebo group. These findings are in line with data presented in the meta-analyses by Morris et al (2019) and Shaffer et al (2019).

Cortisol levels

Substitution of cortisol to early preterm infants (born before 28 weeks of gestation) is established in literature and may help improving regulation of metabolism and inflammatory systems. Cortisol deficiency was nevertheless not considered as an inclusion criterion or a stratification factor in the PREMILOC pivotal clinical trial. Heckmann et al 1999 presented data on distribution of cortisol levels and it appears that close to half of the patients in PREMILOC had values above their proposed reference range. Thus, it is questionable if the anticipated mode of action is applicable for most patients. Renolleau et al (2019), based on PREMILOC data, showed a great variety in cortisol levels at baseline, and an association between cortisol levels and increased risk for GI perforations, and grade 3-4 (severe) IVH in the HC group. Thus, subjects without cortisol deficiency treated early with low-dose HC might be of an increased risk for these (and other serious) adverse events. To further elaborate on risks related to treatment of non-cortisol deficient patients, the applicant has presented safety data divided by cortisol levels at D0. Cortisol levels are available in 111/172 (64.5%) of the

infants born before 26 wks PMA and 223/345 (64.6%) of the infants born > 26 weeks PMA. Based on the data presented it could not be excluded that some safety concerns i.e., infections/sepsis, GI perforations, NEC, hyperglycaemia and IVH are not related to increased cortisol levels during early HCHS treatment in infants with cortisol levels above median at birth/D0. Considering that these events already appear more commonly reported in the HC treated infants compared to placebo any additive effect due to un-physiological levels should be avoided.

3.3.11. Conclusions on clinical safety

Some of the differences in the AE profile between the two treatment groups in infants born < 26 weeks PMA of importance for the B/R balance remains. Firstly, during the on-treatment period (D1-D10) fatal events were more commonly reported in the HCHS treated infants born <26 weeks PMA compared to placebo. The main reason for fatal events was IVH and more patients in the HCHS groups of neonates reported fatal IVH events compared to the placebo group. Furthermore, during on-treatment period, Infections and infestations driven by sepsis and neonatal sepsis were more commonly reported in infants born < 26 weeks PMA treated with HCHS compared to placebo.

During the off-treatment period (D11 to 36 wks PMA), GI disorders and especially NEC was reported more commonly in infants born < 26 weeks PMA compared to placebo. Off treatment, in the entire HC population also IVH were more commonly reported in the HC group compared to placebo.

There remains also an important uncertainty regarding the safety profile for use of early low-dose HC treatment in infants with adequate cortisol levels at baseline.

3.4. Risk management plan

The applicant submitted an RMP version 0.2 as part of this application.

3.4.1. Safety specification

3.4.1.1. Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP version 0.2:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Serious gastrointestinal disorders (including gastrointestinal perforations and Necrotizing colitis (NEC)) Intraventricular haemorrhage
Important potential risks	None
Missing information	Long-term safety

3.4.1.2. Discussion on safety specification

Although the substance is well known, safety concerns related to the novel intended population and indication must be considered.

Upon request, the risk for serious GI disorders (including GI perforations and NEC) and IVH were included as important identified risk. This is acknowledged. However, in addition 'hypertrophic cardiomyopathy' should also be included as an important potential risk. Further, the missing

information of long-term' safety should be removed from the RMP as the safety database is considered sufficient in size, and the length of follow-up sufficient given the intended (short-term) use of the product.

3.4.1.3. Conclusions on the safety specification

Having considered the data in the safety specification,

It is considered that the following issue should be addressed: **'**hypertrophic cardiomyopathy' should be added as an important potential risk in the RMP.

3.4.2. Pharmacovigilance plan

3.4.2.1. Routine pharmacovigilance activities

The applicant proposed follow-up questionnaire (draft version) and periodic cumulative review of 'GI perforation', 'NEC' and 'IVH'. Follow-up questionnaires could be endorsed since CHMP concluded that further evaluations of these risks during the on-treatment period are warranted since available data show that the risk for serious gastrointestinal events including GI-perforation/NEC, intraventricular bleedings and sepsis might have been enhanced by HCHS treatment, especially in the population born < 26 weeks PMA. The applicant is reminded that review of safety concerns included in the RMP should be presented in future PSURs so there is no need to specifically state in the RMP that periodic cumulative review will be performed.

PhV activities regarding 'hypertrophic cardiomyopathy' are not proposed by the applicant as they consider that inclusion of 'hypertrophic cardiomyopathy' as a safety concern is not necessary. However, the CHMP conclusion is that the RMP should be updated to include 'hypertrophic cardiomyopathy' as an important potential risk. Therefore, the applicant is again requested to discuss and propose PhV activities for this important potential risk (also see section 3.4.2.2. *Additional PhV activities*).

3.4.2.2. Additional PhV activities

No additional PhV activities were proposed by the applicant for further characterisation of any safety concern. In addition, the CHMP conclusion is that the RMP should be updated to include 'hypertrophic cardiomyopathy' as an important potential risk.

In conclusion, the applicant should assess and discuss whether registry-based study could be feasible for further characterisation of safety concern 'hypertrophic cardiomyopathy'. The applicant should provide information on registries that could be used, with special emphasis on existing ones, as well as which outcomes, comparator or study design would be feasible to distinguish a potential drug-effect vs. morbidity as the result of pre-term birth.

3.4.2.3. Overall conclusions on the PhV plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the important identified risks of the product. However, the applicant should assess and discuss whether registry-based study could be feasible for further characterisation of safety concern 'hypertrophic cardiomyopathy'. The applicant should provide information on registries that could be used, with special emphasis on existing ones, as well as which outcomes, comparator or study design would be feasible to distinguish a potential drug-effect vs. morbidity as the result of pre-term birth.

3.4.3. Risk minimisation measures

3.4.3.1. Routine risk minimisation measures

The applicant proposed routine RMMs for important identified risks GI perforation and IVH, which is endorsed.

RMMs regarding 'hypertrophic cardiomyopathy' are not proposed by applicant as it is considered that inclusion of 'hypertrophic cardiomyopathy' as a safety concern is not necessary. However, the CHMP conclusion is that the RMP should be updated to include 'hypertrophic cardiomyopathy' as an important potential risk. Following PRAC discussion, it was concluded that additional RMMs are not considered necessary for this risk considering pre-term infants are already under close monitoring in the hospital setting during hydrocortisone administration. Thus, the applicant should include only routine RMMs for 'hypertrophic cardiomyopathy' in the part V of the RMP.

3.4.3.2. Additional risk minimisation measures

Table 33: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Serious Gastrointestinal disorders (including gastrointestinal perforations and NEC)	Routine risk minimisation measures: Summary of Product Characteristic (SmPC) sections 4.4, 4.5 and 4.8 Package Leaflet (PL) sections 2 and 4 Sections 4.4 and 4.5 recommend avoiding concomitant administration of NSAIDs in preterm newborns treated with hydrocortisone unless the benefits outweigh the increased risk. In this case, patients should be monitored for possible symptoms of gastro-intestinal perforation and NEC. In addition to these recommendation measures, SmPC section 4.8 gives further details on the risk of gastrointestinal perforation and NEC to improve the understanding the risk and preparing for clinical measures to address it. PL section 2 and 4 contain adequate recommendations regarding this topic for the patient Prescription only medicine and use in hospital setting. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up form for Necrotizing colitis/Gastrointestinal perforation (see Annex 4). Additional pharmacovigilance activities: None

Important identified risk: Intraventricular haemorrhage	Routine risk minimisation measures: Summary of Product Characteristic (SmPC) sections 4.8 Package Leaflet (PL) sections 4 SmPC section 4.8 gives further details on the risk of intraventricular haemorrhage to improve the understanding the risk and preparing for clinical measures to address it. PL section 4 contains adequate recommendations regarding this topic for the patient Prescription only medicine and use in hospital setting. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted Follow-up form for Intraventricular haemorrhage (see Annex 4) Additional pharmacovigilance activities: None
Missing information: Long-term safety	Routine risk minimisation measures: Summary of Product Characteristic (SmPC) section 5.3 SmPC section 5.3 gives further details on the long-term impact on neurodevelopment to improve the understanding the current knowledge on this risk and preparing for clinical measures to address it. Additional risk minimisation measures: Patient alert card, announced via a Direct Healthcare Professional Communication (DHPC).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Periodic cumulative reviews of long-term safety. Additional pharmacovigilance activities: None

Regarding long-term safety, the proposed DHPC by the applicant contains general information on long-term safety as missing information and is generally considered an introduction to the patient card. On the other hand, the patient card is described to be a model of communication between patients' parents and healthcare providers included in the patients' care ("That the patient card must be carried by the patient's parents and presented to the healthcare professionals who will follow the infant, including specialist in case of non-routine health problems"). It remains unclear if the patient card is therefore directed primarily at the patients' parents or other healthcare professionals. It is also proposed that patient card contains a reminder of the importance of reporting any adverse reactions, which is information that is already present in the PIL.

In general, long-term safety as missing information in the RMP warrants further characterisation, which can include routine (e.g. follow-up questionnaires) and/or additional PhV activities (e.g. post-authorisation safety studies (PASS)). However, risk minimisation measures, especially additional risk minimisation measures such as patient card, are not considered applicable since they are defined as an intervention intended to prevent or reduce the occurrence of **adverse reactions** associated with the exposure to a medicinal product, or to reduce their severity or impact on the patient should an adverse reaction occur. Documents in lay language for general public (e.g. patient card) are described: *"lay language documents should contain the competent authority's recommendations and advice for risk minimisation for patients and should be accompanied by relevant background information".* As per GVP Module XV (Rev. 1), DHPC is used to communicate information on important identified or potential risk, which has significant impact on clinical practice, to healthcare professionals. According to the available data, no such information is identified for long-term safety. In addition, as the safety database is overall considered by the CHMP to be sufficient in size, and the length of follow-up sufficient given the intended (short-term) use of the product, the CHMP thus concluded that the missing information of long-term safety should be removed from the RMP. Therefore, dissemination of DHPC and introduction of patient card for missing information long-term safety are not applicable in this case.

3.4.3.3. Overall conclusion on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that:

The proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s). The applicant should include routine risk minimisation measures for important potential risk 'Hypertrophic cardiomyopathy' in the Part V of the RMP.

3.4.4. PRAC outcome

Overall, the PRAC supported the assessment of the pharmacovigilance plan and risk minimisation measures as detailed in the assessment report. In addition, the PRAC concluded based on available data that routine RMMs are sufficient to address the safety concerns proposed for inclusion in the RMP.

Besides, the PRAC highlighted that the proposed discussion on feasibility of a registry-based study should not only address the missing information 'Long-term safety' but also the important potential risk 'Hypertrophic cardiomyopathy'. The PRAC also recommended to clarify which specific safety outcomes are expected to be covered by the safety concern 'long-term safety' (e.g. neurodevelopmental disorders) as it may have a significant impact on the type of study and, consequently its feasibility. In particular, the applicant is requested to discuss how the effect of pre-term birth on child outcomes of interest could be differentiated from any potential effects caused by the treatment with hydrocortisone.

In conclusion, the RMP for hydrocortisone in the proposed indication could be considered acceptable provided that an update to RMP version 0.2 and satisfactory responses to the questions detailed in the joint CHMP-PRAC D150 overview assessment report is submitted.

3.4.5. Conclusion on the RMP

Overall, the safety database is considered sufficient in size, and the length of follow-up sufficient given the intended (short-term) use of the product. The CHMP therefore recommended to remove long-term safety as a missing information.

The CHMP also considered that the RMP could be acceptable provided an updated RMP and satisfactory responses to the list of outstanding issues below is submitted.

The public summary of the RMP should be updated accordingly.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

Based on the fact that there is no centrally approved medicinal product available for BPD and that the product is for paediatric use only, the PRAC is of the opinion that a separate entry in the EURD list for hydrocortisone is needed, as it cannot follow the already existing entries for hydrocortisone. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

The applicant did request an alignment of the PSUR cycle with the international birth date (IBD) which is 05/08/1952.

4. Benefit/risk assessment

4.1. Therapeutic context

4.1.1. Disease or condition

Bronchopulmonary dysplasia (BPD) is a chronic form of injury to the lungs caused by barotrauma and oxygen injury in preterm infants requiring ventilation. It is the most common chronic lung disease of infancy and a major cause of neurodevelopmental impairment, long-term breathing problems, and mortality. BPD is characterised by fewer but larger alveoli, mild fibrosis, and persistent inflammation that plays a key part in its pathogenesis.

4.1.2. Available therapies and unmet medical need

Although there are certain therapies (e.g. caffein) used tentatively to ameliorate this condition, there is still no established treatment for BPD. Glucocorticoids are used for preventative purposes although there is a split view in the scientific community on their merits.

4.1.3. Main clinical studies

The PREMILOC study is pivotal in this MAA. It was a prospective, placebo-controlled, randomised, multicentre study initiated by French hospital experts in an academic environment and conducted in France. Following its first publication, two *post-hoc* analyses (Baud 2024 and Héneau 2018) were published. The PREMILOC database was also used for a prespecified secondary analysis (Ronolleau 2021) where the association between baseline cortisol and the effect of HC on prevention of BPD was investigated. In addition, neurodevelopmental outcomes at 2 years of age were presented in separate publications. Furthermore, a number of reviews and meta-analyses have been published and some observational data pointing at current use.

4.2. Favourable effects

The primary endpoint in PREMILOC, alive without BPD was achieved in 60.0% (153/255) in the hydrocortisone (HC) group vs 51.1% (135/264) in the placebo group at 36 weeks PMA (p=0.042). Among the secondary endpoints analysed *post hoc* were neonatal all-cause mortality at 28 days which was apparently similar between the two groups (84.7% and 83.7% in the HC and placebo groups respectively). At year 2 the survival rate was numerically higher (81.2%) in the HC group than in the placebo group (74.6%). At at Day 10 63.9 % was extubated in the HC group and 48 % in the placebo group.

4.3. Uncertainties and limitations about favourable effects

The demonstration of efficacy rests on results from a single pivotal clinical trial and the precision of the primary effect estimate leaves a substantial risk for random error. In addition, there are remaining uncertainties regarding type I error control and study integrity. A quite modest and statistically not compelling effect was recorded on need for ventilatory support at 36 weeks and there is no supportive information on long-term efficacy or else support from secondary endpoints. The robustness of the effect estimate in PREMILOC is thus questioned.

There is limited support from other sources available. Reviews and meta-analysis cannot be used to contextualise PREMILOC as PREMILOC data dominates the databases in these publications. It is uncertain to what extent the results from PREMILOC are relevant for neonatal care today as standard of care has developed over the 10 years that have passed since PREMILOC was conducted. There has been continuing efforts to minimise barotrauma from ventilatory support and consequently reduce the risk for BPD. It is thus uncertain whether the results obtained from PREMILOC could be replicated in a modern setting.

No firm conclusions can be drawn for any secondary endpoints; besides a lack of analyses being predefined, the original analysis plan did not include any multiple tesing procedure. There are also uncertainties with regard to subjects treated early with glucocorticoids other than test drug.

There are no data available on long term efficacy.

The supporting studies referred to are small, old and difficult to interpret. Observational data is difficult to interpret as treated and non-treated populations differs regarding risk factors for BPD. Meta-analyses rests heavily on PREMILOC, this being the only larger randomised study available. Authors of review articles present a split view on the intended treatment.

4.4. Unfavourable effects

Adverse events

Up to 36 weeks PMA, any adverse events (AE) were reported by 89.7% in the HC group and 95.8% in the placebo group. SAEs were reported by approximately 75% in both treatment groups. Higher frequencies of SAEs were noted in the <26 weeks populations (~90% in both treatment groups). Deaths were reported in 47 cases (18.6%) in the HC group and 66 cases (25%) in the placebo group.

During the on-treatment period, fatal events were more commonly reported in the HCHS group (24.4%) compared to placebo (16.7%). The main reason for fatal events were IVH. In the HCHS treated < 26 wks PMA infants fatal IVH events were reported by 12.2% compared to 4.4% in the corresponding placebo group.

Sepsis: Up to week 36 PMA, late onset sepsis or systemic candida infection were reported in higher frequencies in the in the HCHS group (54.9%) compared to the placebo group (45.8%). The

frequencies in the < 26 weeks PMA population were higher in both treatment groups (HCHS: 64.4% and placebo: 54.4%).

Necrotizing enterocolitis (NEC): Up to week 36 PMA, events of NEC were more commonly reported in the HC group (7.5%) compared to the placebo group (4.9%). The difference is larger in the < 26 weeks PMA population (HCHS: 8.5% vs placebo: 2.2%) and especially during the on-treatment period (8.5% vs 1.1%).

Gastrointestinal perforation (GI): Up to week 36 PMA, GI-perforations were reported by 5.5% in HC group and 3.8% in the placebo group. The risk for GI-perforations was correlated to cortisol levels short after birth (Renolleau et al, PREMILOC data).

Hyperglycaemia/insulin requirement: Approximately 40% of the subjects in PREMILOC reported need of insulin treatment during the first two weeks after treatment initiation. The frequency was higher in the < 26 weeks PMA population in both treatment groups (HC: 54.9% and placebo: 61.1%).

Intraventricular haemorrhage (IVH): Up to week 36 PMA, IVH overall (regardless of severity) were slightly more commonly reported in the HC treated group (35.6%) compared to the placebo group (33.0%), especially in infants born < 26 weeks PMA population (HC: 47.6% vs 42.2%). Severe IVH before 40 weeks PMA was reported by ~16% in both treatment groups. The risk for IVH was correlated to cortisol levels short after birth (Renolleau et al, PREMILOC data). The difference between the two treatment groups was more markedly during the off-treatment period, (IVH as PT: 15.0% in HCHS group vs 9.5% with placebo).

Retinopathy: In PREMILOC a higher frequency of the children in the HC group reported retinopathy after 2 years (14.4% in the FUS) than the placebo group (9.2% in the FUS). Most of these events had a grade 1 or 2 ROP (6.2% each) and none in the HC group had a grade 4 ROP.

Hypertrophic cardiomyopathy: In PREMILOC "hypertrophic cardiomyopathy" was reported by one subject in the HC group and none in the placebo group. Furthermore, one subject in each treatment group reported the PT "cardiac hypertrophy" (SOC cardiac disorders).

Safety related to cortisol levels: During either the on-treatment or off-treatment period, the following AESIs that are more commonly reported in the HCHS group with cortisol levels > median compared infants with cortisol levels ≤ median: GI Perforation, NEC (for infants born < 26 weeks PMA), Severe IVH before 40 weeks PMA, Late-Onset Sepsis or Systemic Candida and Insulin Requirement During First Two Weeks of Life/Hyperglycaemia.

Neurological development

2-years data: Normal neurological development measured by a combined Developmental Quotient (DQ) and global neurological assessment was reported in a slightly higher frequency in the HC group (72.7%) compared to the placebo group (70.5%) However, neurodevelopmental impairment was also reported in a slightly higher frequency in the HC group (20%) compared to placebo (18%), whereas moderate to severe neurodevelopmental impairment was reported in a lower frequency in the HC group (7%) compared to placebo (11%).

5-years data (PREMILOC; publication by Trousson et al 2022): Mean score of full-scale IQ was slightly higher in the HC treatment group (91.9 [SD = 13.9]) compared to placebo (86.3 [SD = 15.4]).

4.5. Uncertainties and limitations about unfavourable effects

In PREMILOC, the safety profile clearly demonstrated that the risks for AEs in general were, in both treatment groups, higher in infants born < 26 weeks PMA compared to those born > 26 weeks PMA.

Some of the differences in the AE profile between the two treatment groups in infants born < 26 weeks of importance for the B/R balance remains. Firstly, during the on treatment (D1-D10) period fatal events were more commonly reported in the HCHS treated infants born <26 wks PMA compared to placebo (24.7% vs 16.7%). The main reason for fatal events was IVH and in total, 50% of the fatal events in the HCHS group of neonates born < 26 wks were IVH event compared to 25% in the placebo. Furthermore, during on treatment period Infections and infestations driven by sepsis and neonatal sepsis were more commonly reported in infants born < 26 weeks treated with HCHS compared to placebo (SOC Infections; 36.6% vs 27.8%; neonatal sepsis: 29.3 vs 21.1% and sepsis: 4.9% vs 1.1%).

During the off-treatment period (D11 to 36 wks PMA) GI disorders and especially NEC was reported more commonly in infants born < 26 weeks PMA compared to placebo (HCHS 8.5% vs 1.1% with placebo). Off treatment, in the entire HC population also IVH were more commonly reported in the HC group compared to placebo. However, results of the outcome of IVH events have not clearly been presented.

There remains also an important uncertainty regarding the safety profile for use of early low-dose HC treatment in infants with adequate cortisol levels at baseline. Based on the data presented it is indicated that the risk for some safety concerns including GI perforations and IVH, are increased in infants with cortisol levels > median at D0 (in both treatment groups). Considering that these events already appear more commonly reported in the HC treated infants compared to placebo any additive effect due to un-physiological levels should be avoided.

Table 34: Effects Table for hydrocortisone in BPD.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Alive without BDP at 36 weeks of PMA	Any surviving preterm infant without bronchopulmonary dysplasia at 36 weeks of amenorrhoea. BPD defined as ventilatory support using either mechanical or continuous positive airway pressure (CPAP) ventilation, or spontaneous ventilation with the need for FiO2 ≥ 30%, or spontaneous ventilation with FiO2 < 30% but a failure in oxygen reduction test (Walsh test) showing true oxygen dependency	N %	153/255 (60)	135/264 (51.1)	Uncertainties: there are concerns regarding maintenance of the type I error control in the final analysis of the primary endpoint. In addition, initial concerns with regard to the precision of the primary effect estimate leaving a substantial risk for random error and the lack of statistically compelling support from secondary endpoints remain.	PREMILOC
Unfavourable Effects						
Late onset sepsis or systemic candida infection (AESI)	Up to 36 weeks PMA	%	54.9	45.8	The frequencies in the < 26 weeks PMA population were higher in both treatment groups (HCHS: 64.4% and placebo: 54.4%).	PREMILOC
NEC (AESI)	Up to 36 weeks PMA	%	7.5	4.9	The difference is larger in the < 26 weeks PMA population (HC: 8.5% vs placebo: 2.2%) and especially during the off-treatment period (8.5% vs 1.1%).	PREMILOC
GI-perforation (AESI)	Up to 36 weeks PMA	%	5.5	3.8	The risk for GI-perforations was correlated to cortisol levels short after birth.	PREMILOC, Renolleau et al

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
IVH (PT)	Up to 36 weeks PMA	%	35.6	33.0	in the lower < 26 weeks PMA population (HC: 47.6% vs 42.2%). The difference between the two treatment groups was more markedly during the off-treatment period, (IVH as PT: 15.0% in HCHS group vs 9.5% with placebo); in the lower < 26 weeks PMA population 18.3% vs 13.3%). The risk for grade 3-4 IVH was correlated to cortisol levels short after birth.	PREMILOC, Renolleau et al
Severe IVH before 40 weeks PMA (AESI)	Up to 36 weeks PMA	%	16.2%	15.9%	In the lower < 26 weeks PMA population: HC 28.0% vs placebo 27.8%)	PREMILOC

4.6. Benefit-risk assessment and discussion

4.6.1. Importance of favourable and unfavourable effects

The robustness of the primary effect estimate (alive without BPD at 36 weeks PMA) in PREMILOC is still questioned. The clinical effect seen at 36 weeks was quite modest and statistically not compelling. The latter pertaining to remaining uncertainties whether the final analysis of the primary endpoint owned type I error control. In addition, a critical issue is further concerns over study integrity and whether the decision to stop the trial was made by individuals with knowledge of interim analysis results.

Furthermore, there is no supportive information on long-term efficacy or else support from secondary endpoints. There also remains an important uncertainty to what extent the results from PREMILOC are relevant for neonatal care today as standard of care has developed over the 10 years that have passed since PREMILOC was conducted.

The safety profile presented up to week 36 PMA demonstrates a safety pattern in line with the known risks for neonates due to premature birth and the known safety profile of hydrocortisone. There are, nevertheless, some risks that seems to increase in frequency during treatment with early low-dose HC treatment compared to placebo. These includes sepsis, IVH, NEC and GI perforation. There are also remaining issues pertaining to safety, especially in the subjects with lowest gestational age (< 26 wks) and those with adequate cortisol levels at baseline.

There are three outstanding MO on quality impacting the benefit/risk of the product.

In response to the MO raised at day 120 on the sterilisation of the vial adapters, the applicant has declared the name and address of the vial adapters manufacturer and the details of their sterilisation process but the information on who is responsible for the sterilisation process is still missing.

The product is to be administered with a high accuracy 1ml syringe (not provided with the product); the wording in the SmPC should be updated to ensure it includes all relevant information on the syringe accuracy to ensure an adequate syringe is used by HCP and avoid administration errors.

The applicant should revise how the assay results are reported (mg/per total drug product) and update the assay release and shelf-life specification limits to 95.0-105.5% as per Notice to Applicants, volume 2B. This is key to guarantee adequate active substance content on the finished product, accurate dosing and avoid impact on the product safety and efficacy.

4.6.2. Balance of benefits and risks

Considering that the documented effect is associated with substantial uncertainties and that data indicates a non-negligible increased risk of certain, potentially serious adverse events, the benefit risk balance is considered to be negative.

4.6.3. Additional considerations on the benefit-risk balance

Not applicable.

4.7. Conclusions

The overall benefit /risk balance of Hydrocortisone Aguettant in the prevention of BPD is negative.