CLINICAL TRIAL PROTOCOL

Stop exogenous allergic alveolitis (EAA) in childhood: healthy into adulthood – a randomized, double-blind, placebo-controlled, parallel-group study to evaluate prednisolone treatment and course of disease

Short Title: **Stop EAA**

for Germany

EudraCT: 2013-003689-15

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List of abbreviations

AE	Adverse event
AMG	German drug law (Arzneimittelgesetz)
AR	Adverse reaction
ASP	Application service provider
BAL	Bronchoalveolar lavage
BP	Blood pressure
BSI	Federal Office for Information Security
Bw	body weight
CRF	Case report form
CSUCT	Computerized systems used in clinical trials
DCF	Data clarification form
D_{LCO}	Diffusing capacity of the lung for carbon monoxide
DMP	Data management plan
DPLD	Diffuse parenchymal lung disease
DMC	Data monitoring committee
DSMB	Data safety monitoring board
EAA	Extrinsic allergic alveolitis
EC/IEC	Ethics committee/Independent ethics committee
e-CRF	Electronic case report form
EDC	Electronic data capture
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSI	First subject in
FVC	Forced vital capacity
FVC%	Forced vital capacity in percentage of normal value
GCP	Good clinical practice
GCP-V	GCP regulation
gGT	Gamma-glutamic transferase
GOT	Glutamate oxaloacetate transaminase
HbA_1c	Glycohemoglobin
HP	Hypersensitivity pneumonitis
HRCT	High resolution computed tomography
ICH	International conference on harmonization of technical requirements for registration of pharmaceuticals for human use
IDAT	Subject identification database
IgG	Immunoglobulin G
IMP	Investigational medicinal product
IRB	Institutional review board
ISF	Investigator site file
ISP	Internet service provider
ISRCTN	International standard randomized controlled trial number
INN	International non-proprietary name
ITT	Intention to treat
IZKS	Interdisciplinary centre for clinical trials
LDH	Lactatdehydrogenase
LKP	Clinical Trial Director according (Leiter der Klinischen Prüfung)
MDAT	Medical database
MedDRA	Medical dictionary for regulatory activities terminology
NEA	Emergency power supply
QC	Quality control
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SAS	Statistical analysis system

SDV	Source data verification
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPSS	Statistics program
SSL	Secure Sockets Layer
SUSAR	Suspected unexpected serious adverse reaction
TMF	Trial master file
USV	Uninterruptible power supply

Synopsis

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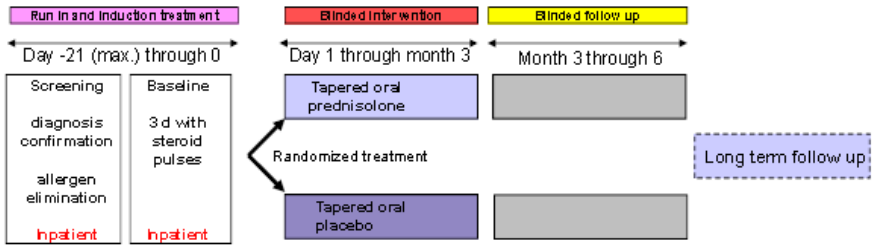
TITLE OF STUDY	Stop exogenous allergic alveolitis (EAA) in childhood: healthy into adulthood – a randomized, double-blind, placebo-controlled, parallel-group study to evaluate prednisolone treatment and course of disease
RATIONALE	The long term course of individuals with exogenous allergic alveolitis (EAA) cannot be predicted individually, although initial allergen removal and steroid treatment appears simple. Some children may have a complicated course; thus all should be assessed, treated and followed systematically.
HYPOTHESIS	Treatment with placebo will not be inferior in terms of Forced Vital Capacity (FVC) improvement than treatment with systemic steroids after 6 months treatment.
OBJECTIVE(S)	Primary objective: To evaluate outcome of EAA at 6 months and compare medium term treatment with systemic steroids or placebo. Secondary objectives: To evaluate the completeness and knowledge of standardized and pedantic allergen elimination in families with a child with EAA. To evaluate the treatment of EAA with systemic steroids compared to placebo at 3 months To evaluate the safety of the treatment of EAA with outpatient usage of systemic steroids compared to placebo
INTERVENTION(S)	Experimental intervention: Placebo Control intervention: Prednisolone Duration of intervention per patient: 3 months Follow-up per patient: 6 months
KEY INCLUSION AND EXCLUSION CRITERIA	Key inclusion criteria: 1. Newly or previously diagnosed but not appropriately treated EAA in children, adolescents and young adults (6 to 25 years). The diagnosis of EAA must be confirmed by independent review of the findings by an expert panel and must be based on the presence of at least 4 of the following findings: * History of appropriate allergen exposure * Restrictive lung function (FVC < 80% predicted for age and FVC/FEV1 < 1) testing, if appropriate for age (usually > 5 y) * Positive serum precipitins for bird/fungus exposed to (other allergens have rarely, if every been demonstrated in children) * Lymphocytosis in BAL (> 20% of cells are lymphocytes) * HRCT showing the characteristic nodular, linear or reticular opacities and ground glass pattern with increased attenuation. * Lung biopsy demonstrating lymphocytic alveolitis, bronchiolitis, and non-caseating histiocytic granulomatas. * Controlled allergen exposure followed by characteristic reaction, including fever, coughing, restriction on lung function, hypoxemia/desaturation at rest or with exercise 2. Unchanged inhaled steroids if on; if off, no plans to introduce them in the following 6 months

	3. Agreement to home visit by independent study physician Key exclusion criteria: Subjects presenting 1 of the following criteria will not be enrolled in the trial: Contraindication for usage of systemic steroids Critically ill patients needing respiratory support Non-compliance with medical treatments and interventions Not appropriate contraception in women of childbearing age, pregnancy and lactation Participation in another trial for EAA during the last 4 weeks or not beyond the time of 4 half-lives of the medication used in the other trial. In the unlikely event a subject is already in another clinical study but not for EAA, that study must be stopped and the subject may be treated according to this protocol; a latency time between the two studies does not appear reasonable, as acute intervention is necessary for EAA. Treatment may be best done in the frame work of this protocol.
OUTCOME(S)	Primary efficacy endpoint: Relative change from baseline through month 6 compared to change from placebo for * forced vital capacity (FVC). Key secondary endpoint(s): Each patient will be classified as a responder or non-responder. A patient is considered as a responder, if the FVC value after 6 months is more than or equal to 93% of the norm values tabulated by Quanjer PH., et al. 2013. Relative change from baseline through month 6 compared to change from placebo for * desaturation with standardized exercise test for children * Borg scale * Quality-of-life * Health economics * Weight for height * Open usage of rescue glucocorticosteroids (mg/kg/6 months) Relative change from baseline through month 3 compared to change from placebo for * forced vital capacity FVC * desaturation with standardized exercise test for children * Borg scale * Quality-of-life * Health economics * Weight for height * Open usage of rescue glucocorticosteroids (mg/kg/6 months) Assessment of safety: * Adverse events * Clinical laboratory values (GOT, Creatinine, gGT, blood count, differential, LDH, HbA1c) * Safety values including blood pressure, height.
STUDY TYPE	prospective, multicentre, randomized, double-blind, placebo controlled trial

STATISTICALANALYSIS	Efficacy: The primary analysis variable is the improvement in FVC (difference after 6 months and baseline). The 6 months and baseline FVC values will be given in percent deviation from the norm values tabulated by Quanjer PH., et al. 2013. A difference between the changes in placebo and active treatment is considered not significant if FVC differences are < 7%. The working hypothesis of the study is that the placebo intervention is not inferior to the prednisolone intervention. Description of the primary efficacy analysis and population: The improvement in FVC will be compared between groups within an analysis of covariance (ANCOVA). Treatment will serve as a fixed factor and the baseline FVC value as a covariate. The primary analysis population will consist of all randomized patients without any major protocol violations. The two-sided 90% confidence interval for the treatment difference will be calculated. Sensitivity analyses will be performed by analysing the same analysis model for all randomized patients. Additionally, the primary parameter will be analysed by ANCOVA with additional terms for sex and height. Centre effects will be explored by descriptive statistics. Safety: Adverse events will be coded by MedDRA and analysed by descriptive methods. Laboratory values will be displayed by sample characteristics over time and compared between groups by exploratory p-values. Secondary endpoint(s): Secondary endpoints will be displayed by descriptive statistics and compared between groups by exploratory p-values.
SAMPLE SIZE	To be assessed for eligibility: **(n=60)** To be allocated to trial: **(n=45)** To be analyzed: **(n=40)**
TRIAL DURATION	First patient in to last patient out (months): 24 Duration of the entire trial (months): 27 Recruitment period (months): 18
PARTICIPATING CENTERS	**About 40 trial sites are planned to participate**
RELEVANCE	• World-wide the first, randomized controlled trial in children with interstitial lung disease ever and the first clinical project, unifying several pediatric pneumology sites from different European countries into a common project • Direct improvement of the health of children with EAA across Europe and wide spread distribution of state of the art protocols to diagnose and treat EAA in childhood. • Substantial increased awareness of the child-EU-project in the pediatric pneumology area • Strengthened position of the European Pediatric Pneumology within the international Pneumology Scene
STUDY FLOW CHART	

Trial schedule

Table 1

Visit	Inpatient	Inpatient	Inpatient	Inpatient	Visit 1	Visit 2 and	Visit 3	Telephone contact trial day 126 (119, 133)[j]	Visit 4	Long term follow up
Action	Screening, diagnosis confirmation, allergen elimination	Baseline	Steroid pulse Treatment	Discharge	1 month	Personal contact 2 month	3 month		6 month	annually
Trial day	-21 to -2	-4 to -2	-2 to 0	1	28 (21, 35)	56 (49, 63)	84 (74, 94)		168 (148, 188)	annually
Demographics (sex, age, race)	X									
Patient information, informed consent	X									
Previous and concomitant diseases	X				X					X
Previous and concomitant treatments	X				X					X
Inclusion/exclusion criteria	X									
Randomization [a]	X									
Medication supply				X						
Expert allergen consultation and education [b]	X (in hospital)					X (at home)				
Physical examination	X				X	X				
Pregnancy test[k]	X								X	
Vital signs (Height, weight, BP, pulse, temp) [c]	X				X	X				
Blood sample [d]			X							
FVC % predicted (spirometry) [e]	X*	X		X	X	X	X		X	X
O2-saturation, respiratory rate and Borg scale[f]	X*	X		X	X	X	X		X	X
Standardized exercise testing[g]	X*						X		X	
HRCT	(X)									
Health economics[h]		X					X		X	X
Quality-of-life[i]		X					X		X	X
Adverse events				X	X	X	X		X	
End of trial (final visit)									X	Build a cohort into adulthood

X* Test must be done before first drug dosing

[a] Randomization must occur after all inclusion and exclusion criteria are met directly after consent to the study is given and at least 1 week before first dose of oral prednisolone.

[b] SOP for allergen elimination will be provided

[c] Weight and height will be measured with shoes and clothes off. Vital signs will be collected after the patient has been at rest for 5 minutes.

[d] Blood sample should include: Blood count with differential, Potassium, GOT (Aspartate aminotransferase), gGT, Creatinine, LDH (Lactate dehydrogenase), glucose, HbA1c.

[e] SOP will be provided.

[f] Measurement of O_2-Saturation, respiratory rate and O_2 flow (if necessary) in awake patient at rest:

If not on O_2: after 5 min at rest, room air, then measure twice over 1 min. each, at least 1 min. apart

If on O_2:

- BEFORE withdrawal (after 5 min at rest with steady state O_2 supplement, then measure over 1 minute)
- Then withdraw O_2 to obtain steady state O_2-Sat. in room air (at least 30 seconds without change). Then measure twice over 1 min. each, at least 1 min. apart. If falls below SpO_2<80% place back in oxygen and note as <80%.

Borg-Scale: assessment of dyspnea (0 – 10: 0 = no dyspnea at all, 5 = severe dyspnea, 10 = extremely severe dyspnea)

[g] Standardized exercise testing: SOP for 6 min running test will be provided

[h] Health economics assessment with the use of a special questionnaire which has to be filled out by the parents

[i] Quality of Life assessment with the use of the questionnaire PedsQL for different age groups

[j] Telephone contact: Parents must be asked for symptoms and status of allergen elimination

[k] Pregnancy test only has to be performed in girls of childbearing age and only if sexual relations are known or probable. It is at the discretion and responsibility of the attending physician to decide, whether a pregnancy test is necessary or not

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1. INTRODUCTION

1.1 Scientific background

Exogenous (extrinsic) allergic alveolitis (EAA) is a complex syndrome with a broad spectrum of clinical presentations, disease intensity, and natural course (Blatmann 2012). In the English literature the entity is also called hypersensitivity pneumonitis.
The diagnosis is based on history, restrictive lung function, and radiographic, and lung lavage or sometimes biopsy findings.

The problem
Treatment primarily is based on removal of the patient from the suspected etiologic exposure. At first glance this may be very easy and straight forward in many patients. However in some it is cumbersome has to be controlled by treating physicians and may unfortunately remain incomplete in clinical practice. Sometimes, and this cannot be predicted, allergen exposure obviously is reported to be not given, but symptoms remain or resolution is incomplete. The exact cause cannot be identified or eliminated, as it remains obscure.

Overall, unfortunately, in about 25% and not individually or prospectively identifiable patients, disease activity for some reasons does not resolve (Griese et al 2013). These patients need to be identified early. As the overall number of children with this entity is rather low, this is only possible when all subjects are prospectively followed to identify those with a problem.

Additional problems may be associated with glucocorticoid treatment. This is given very frequently, however may only be required in more severe cases. A huge disadvantage of glucocorticosteroid treatment is that in case of a reduced but continuing allergen exposure, the inflammatory activity is ongoing, maintaining chronic disease and slow development of fibrosis in the lungs. At the same time symptoms and lung function are improved and the clues to allergen removal are disguised.

Compared to many other allergens, exposure to bird´s allergen (Bird fancier's EAA, pigeon breeder's disease) appears to have a worse prognosis (Minder 2005). EAA from bird allergens is also the primary cause in children (see below). Frequently high levels of bird antigens can be detected in the home environment over prolonged time periods after bird removal and cleaning (Craig 1992). Several groups have noted chronic, progressive, and fatal cases of EAA secondary to bird antigen exposure (Grammer 1990, Remy-Jardin 1993, Zacharisen 2002). In some series of chronic pigeon breeder's lung a high mortality (29 percent at five years) was observed (Pérez-Padilla 1993).
Nowadays on the lung transplant waiting lists in Munich and Hannover are at any point in time about 4 to 6 young adult patients with end stage lung disease from EAA awaiting lung transplant (personal communication). In Hannover, 26 patients with EAA were listed in the last 4 years; 11 are transplanted meanwhile, 4 have died (personal communication). Thus a significant real long term problem exists which may be tackled by the approach suggested.

1.2 Trial rationale

The impact
Thus it is clear that appropriate treatment including secondary prophylaxis is currently not widely implemented in an efficient way. A significant source of morbidity, likely earlier mortality in adulthood, psychosocial and socio-economic burden exists despite principal diagnosis of the entity. This and a late diagnosis in up to a quarter of the children with EAA (own data) and inappropriate steroid treatment must be overcome to improve management of EAA. We also hypothesize that prednisolone treatment may mask appropriate allergen removal and will tend to drive the patient into chronic lung disease, due to continuous allergen firing of the disease process.

This European-wide study will address these issues and will help to implement an exhaustive procedure for everyday care of this most important pediatric interstitial lung disease.

- We will locate all pediatric EAA patients by monthly European wide alerts to all institutions treating children
- We will supply up-to-date information on the diagnosis of EAA and have the diagnosis peer-reviewed
- We assist with allergen identification; verify removal of the allergen exposure and secondary exposure prophylaxis
- The protocol will allow one initial treatment to help rapid recovery from hypoxemia and it will offer randomized, placebo-controlled medium term treatment with prednisolone.
- We will collect the albeit small cohort of all newly diagnosed children from the beginning, which is important as it cannot be predicted who will have a complicated course and who will not.
- We will externally verify removal of the allergen exposure by a home visit
- We will be able to make a decision on the benefit and risks of prednisolone treatment in EAA
- We will build up a long term cohort of children for follow up into adulthood within the European Pediatric Pneumology community based on the child-EU-project
- We will prevent patients from running early into chronic respiratory failure, early death or lung transplant

1.3 Treatments and rationale for dose selection

EAA – own and other studies

In a recent survey on the incidence and classification of pediatric diffuse parenchymal lung diseases (DPLD, interstitial lung diseases) in Germany, the major contributor was EAA, making up 30% of all cases over all age groups and among 65% of all cases among the diseases occurring beyond infancy (Griese 2009). Thus EAA is the major interstitial lung disease in children. This is in contrast to the French cohort where 5 cases of children were reported, which comprised only those cases reported to a register (Nathan 2012).

In a recent study we investigated twenty-three children with confirmed pediatric EAA (age 9.4 y (4.4-15.1)), prospectively collected in the nationwide survey and submitted to us for evaluation (Griese et al 2013). The children presented with dyspnoea at rest or with exercise, mean FVC was 39% of predicted, seven of the 23 children already had a chronic disease state at presentation, including clubbing. Clubbing predicts a worse outcome in adults (Sansores 1990). IgG against bird was elevated in 20, and against fungi in 15. Except 2 (those treated in our center), all children were treated with prolonged courses of systemic steroids. Outcome was not favorable in all cases treated with steroids, i.e. chronic hypoxemia and very prolonged steroid usage were present in several cases.

EAA in children, although relatively common for pediatric pulmonologists but seen infrequently by many other physicians treating these children, may not be recognized and treated appropriately. A recent study from Denmark reported 19 pediatric cases who were treated with 15 courses (8–34) of monthly intravenous methylprednisolone pulses in resolved cases. This extremely invasive therapy was not sufficient for the vast majority (92%) of children, necessitating additional therapy in all but 1 patient. Nevertheless, normal values of FEV1 or FVC were not reached (Buchvald 2011).

Medication and previous studies

Glucocorticoid treatment is currently prescribed for all symptomatic pediatric patients with EAA (Griese 2009). Prednisolone may accelerate recovery; however, the long-term outcome appears not to be altered (Kokkarinen 1992, Mönkäre 1983).

In this study we propose to use a single three day boost of steroids in order to allow a rapid symptomatic recovery (as described below) of the children and then randomize to a relatively low dose taper of prednisolone, as frequently done in current practice.

To our knowledge there are no randomized trials, even in adults (in patients) with EAA due to bird allergens.

One study of 93 patients with farmer's lung compared patients treated with glucocorticoids for 4 or 12 weeks to control patients treated with antigen avoidance alone (Mönkäre 1983). Symptom resolution was more rapid among the glucocorticoid-treated groups, but no differences in the course of disease among the three

groups were noted after six months. The 12 week glucocorticoid regimen offered no advantage over the four week regimen. This study is limited by the fact that the non-glucocorticoid-treated group was less severe and that the study was not blinded.

A trial of 36 persons with acute farmer's lung randomized patients to eight weeks of treatment with either prednisolone or placebo (Kokkarinen 1992). After one month, there was a significant improvement in DLCO in the prednisolone-treated group, but no statistically significant differences in FVC, FEV1, or DLCO were found after that time until follow-up was terminated at five years.

There are yet no randomized controlled trials in pediatric EAA patients at all.

1.4 Summarized risk-benefit assessment

The need for a trial:

Based on our previous studies we know that at least 50% of the children with newly diagnosed EAA are not appropriately diagnosed and a majority is treated in a non-standardized manner, very much relying on long term usage of systemic steroids (Griese 2009). This strategy has down-sides, especially the blurring of accurate allergen removal. This will result in chronic lung disease driven by long term allergen exposure, as described above.

With this study we will introduce a rigorous and externally controlled program to identify and remove offending allergens. This very likely will result in dissolution of the driving force for chronic lung disease; in the placebo arm not treated with steroids we will be able to see the efficacy of allergen removal in the short term, and during the latter part, when all subjects are off medication this can be identified in the prednisolone arm. Taken together the study design will allow an unbiased judgment of the overall efficacy of allergen removal in pediatric EAA and also of the value and risks of medium term prednisolone treatment.

So far there are no randomized trials in pediatric EAA, cases and series available demonstrate this unfortunate situation.

Summarized risk-benefit assessment:

Although controlled studies are lacking in children, corticosteroids are considered to be effective in EAA in improving symptoms and reversing radiographic and lung function abnormalities (Fan 2002). However the long-term outcome appears to be unchanged by glucocorticoid treatment (Kokkarinen 1992).

It is known that the treatment with systemic steroids in general can be followed by a variety of side effects and is not tolerated in all patients (Saag 2013).

Common side effects of systemic steroid therapy in general are: increased risk for infections, Cushing syndrome, low serum potassium, fluid retention, mood changes, growth retardation, hypertension, peptic ulcerations, reduced wound healing, muscle weakness. Therefore during the study physical examination is performed and serum potassium, renal function and blood pressure are monitored.

The side effects of steroid therapy are dependent on dose and duration of therapy. There is a large body of evidence from many different diseases that high-dose pulse steroids have fewer side effects than systemic steroids at the same cumulative dose but given daily over prolonged periods of time. Generally short term pulse steroid therapy is considered save in pediatrics with very little risk (Reinhardt 2004). In the retrospective chart review of Buchvald 2011 patients were treated with monthly high dose intravenous steroid pulses over a median time of 15 months, without major steroid induced side effects. In the study proposed here, patients receive only one single steroid pulse over three days. So the risk for major side effects is considered to be very low due to the short time of high dose steroid treatment.

Concerning the low dose oral prednisolone following the steroid pulse it is important to know, that in current practice steroids are often used in EAA treatment, either as a pulse or as oral low dose therapy. With the dose used in this study decreasing over three months the risk of developing a Cushing syndrome is present but relatively low; in particular with the avoidance of inhaled steroids over longer time courses and close monitoring of potential side effects we believe that the potential benefit of the treatment outweighs risks definitely.

The investigator will be informed about any relevant or new finding including AEs relating to treatment with the investigational medicinal product.

2. TRIAL OBJECTIVES

2.1 Primary objective

The primary objective of the trial is to evaluate outcome of EAA at 6 months and compare the medium term treatment with systemic steroids or placebo.

2.2 Secondary objectives

The secondary objective(s) of the trial is/are

a) To evaluate the completeness and knowledge of standardized and pedantic allergen elimination in families with a child with EAA.
b) To evaluate the treatment of EAA with systemic steroids compared to placebo at 3 months.
c) To evaluate the safety of the treatment of EAA with outpatient usage of systemic steroids compared to placebo

This study is a prospective, multicenter, randomized, double-blind, placebo-controlled parallel-group study.

3. TRIAL DESIGN

3.1 Trial duration and schedule

The duration of this trial is expected to be 27 months. The subject recruitment proposed to start in Q4/2013 and should last as long as possible, at least till the end of the chILD-EU project or longer if possible. The actual overall trial duration or subject recruitment period may vary from this time period.

3.2 Number of subjects

It is planned to assess 60 subjects for eligibility, to allocate 45 subjects to the trial and to analyse 40 subjects.
Recruitment and treatment of subjects is expected to be performed in > 40 trial centers.

3.3 Primary endpoint

The primary endpoint is the relative change from baseline through month 6 compared to change from placebo for forced vital capacity (FVC).

3.4 Secondary endpoints

Each patient will be classified as a responder or non-responder. A patient is considered as a responder, if the FVC value after 6 months is more than or equal to 93% of the norm values tabulated by Quanjer PH., et al. 2013.

Further secondary endpoints are:

Relative change from baseline through month 6 compared to change from placebo for

* desaturation with standardized exercise test for children
* Borg scale
* Quality-of-life
* Health economics
* Weight for height
* Open usage of rescue glucocorticosteroids (mg/kg/6 months)

Relative change from baseline through month 3 compared to change from placebo for

* forced vital capacity (FVC)
* desaturation with standardized exercise test for children
* Borg scale
* Quality-of-life
* Health economics
* Weight for height
* Open usage of rescue glucocorticosteroids (mg/kg/6 months)

3.5 Measures taken to minimize/avoid bias

3.5.1 Randomization

Patients will be allocated to the two treatments, i.e., oral prednisolone and placebo, in a ratio of 1:1 by central randomization within each age group.

The randomization procedure will not consider the sex of the patients, since no sex-specific responses to prednisolone therapy have been reported yet and are not expected. The randomization list will be generated by the IZKS Mainz using a pseudo-random number generator to ensure that the resulting treatment allocation will be both reproducible and non-predictable.

During inpatient treatment each patient to be included will receive the next consecutive random/ patient number from a block of randomization numbers. Study medication will be packed and blinded according to the random list. Each patient medication box will be sent together with the sealed unblinding codes (i.e. envelopes) to the sites. The investigator has to take care that each patient will be provided with the study medication box bearing the correct randomization number.
The randomization list is to be kept confidential and is only accessible to authorized personnel until the code is broken. At the end of the trial, any emergency opening of the envelopes will be controlled after collecting the explanations for unblinding and checking the unused treatment units. The code will be broken regularly only at the end of the study after freezing the statistics database (by checking the data, recording any protocol violations etc.) allowing the collected data to be analyzed.

3.5.2 Blinding

Blinding will be achieved by providing the study-specific prednisolone and placebo tablets in blinded capsules.

In the case of a medical emergency requiring identification of the treatment taken by the patient, the investigator has the right to open the respective envelope, but every effort should be taken to avoid unblinding of patients except the information will be needed for the emergency treatment. Opened envelopes have to be signed, dated and the reason for unblinding has to be documented. The envelope has then to be filed in the patient notes and the sponsor and/or the responsible monitor has to be informed. Unblinded patients have to be withdrawn from the study. No other reason than an emergency may justify unblinding. After unblinding the investigator has also to note the date, time and reason in the source documents.
The unblinding codes are not to be opened by the investigator at the end of the trial.

3.6 Selection and withdrawal of subjects

No subject will be allowed to enrol in this trial more than once.

3.6.1 Inclusion criteria

Subjects meeting all of the following criteria will be considered for admission to the trial:

1. Newly or previously diagnosed but not appropriately treated EAA in children, adolescents and young adults, aged between 6 and 25 years. The diagnosis of EAA must be confirmed by independent review of the findings by an expert panel and must be based on the presence of at least 4 of the following findings:
* History of appropriate allergen exposure
* Restrictive lung function (FVC < 80% predicted for age and FVC/FEV1 < 1) testing, if appropriate for age (usually > 5 y)
* Positive serum precipitins for bird/fungus exposed to (other allergens have rarely, if every been demonstrated in children)
* Lymphocytosis in BAL (> 20% of cells are lymphocytes)
* HRCT showing the characteristic nodular, linear or reticular opacities, and ground glass pattern with increased attenuation.
* Lung biopsy demonstrating lymphocytic alveolitis, bronchiolitis, and non-caseating histiocytic granulomatas.
* Controlled allergen exposure followed by characteristic reaction, including fever, coughing, restriction on lung function, hypoxemia/desaturation at rest or with exercise
2. Unchanged inhaled steroids if on; if off, no plans to introduce them in the following 6 months
3. Agreement to home visit by independent study physician

3.6.2 Exclusion criteria

Subjects presenting with any of the following criteria will not be included in the trial:

- Contraindication for usage systemic steroids
- Critically ill patients needing respiratory support
- Non-compliance with medical treatments and interventions
- Women with childbearing potential and not practicing a medically accepted contraception during the trial and a positive pregnancy test (serum or urine) before and at the end of the trial. Reliable contraception are systematic contraceptives (oral, implant, injection) and diaphragm or condoms with spermicide.
- Pregnancy and lactation.
- Participation in another trial for EAA during the last 4 weeks or not beyond the time of 4 half-lives of the medication used. In the unlikely event a subject is already in another clinical study but not for EAA, that study must be stopped and the subject may be treated according to this protocol; a latency time between the two studies does not appear

reasonable, as acute intervention is necessary for EAA. Treatment may be best done in the frame work of this protocol.

3.6.3 Withdrawal criteria

Subjects can withdraw their consent at their own request without given reasons at all time during the trial. This should be without disadvantages for the subject. However the investigator should try to perform a final visit to get concluding findings of investigation.

Subjects may be withdrawn from the trial for the following reasons

- At their own request or at request of the legal representative
- If, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being
- If there occur major side effects of the study medication, which make it irresponsible to continue with the study medication.
- If the patient's condition deteriorates in a way, that an intensification of the therapy is necessary and additional open steroid treatment is not sufficient to alleviate the condition.
- For women, if it becomes known that the subject is pregnant.

The investigator decides about withdrawal of subjects from the clinical trial in case of occurrence of criteria mentioned above.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records. In case of withdrawal of a subject at his/her own request, as far as possible the reason should be asked for and documented. The subject must be followed up and as far as possible, all examinations scheduled for the final trial day should be performed and documented.
All on-going serious adverse events of withdrawn subjects have to be followed up see 6.2.1.3.

Withdrawn subjects will not be replaced.

3.6.4 Premature closure of the clinical trial

The following reasons the whole trial may be discontinued at the discretion of the sponsor:

- New risks for subjects become known.
- Inefficacy of the trial medication becomes evident.
- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected increase in the incidence of known AEs.
- Medical or ethical reasons affecting disadvantageous the continued performance of the trial.

The ethic committees (EC) and the competent authority must then be informed. Should the trial be closed prematurely, all trial material must be returned to or fetched by the monitor.

4. TRIAL TREATMENTS

4.1 Identification and elimination of EAA Allergens

A) Identification of possible allergens with the following questions (shortly after diagnosis has been made):

	Yes	No	Comment
Birds or other pets at home or in the garden?	O	O	
Bird cage/chicken house/pigeon loft at home or in garden?	O	O	
Down feathers in bed/clothing?	O	O	
Fungi at home?	O	O	
Humid stonework, wallpaper, furnishing or carpet?	O	O	
Water container/tabletop fountain/swimming pool/whirlpool at home?	O	O	
Contact to hay/straw/feed grain?	O	O	
Air condition at home?	O	O	
Potted plants at home?	O	O	
Contact to organic waste or compost?	O	O	

A ground plan of house and garden has to be drawn together with the patient or his parents with marking the information asked above; please send this plan to the study center.

B) High quality and standardized serological allergen/precipitin identification in experienced labs, e.g. Prof. Behr, Internal Medicine, Klinikum Großhadern, LMU or Prof. Sennekamp, Bonn.
Elimination of antigen (shortly after diagnosis has been made):

- If birds or other pets at home
  - give them away, also the birdcage
  - cleaning of all tissues (i.e. carpet, curtains etc.)
- elimination of down feathers in bed/clothing
- no water container/nebulizer
- no swimming pool, whirlpool, tabletop fountain
- avoid contact to hay, straw, feed grain
- fungi:
  - humidity in room air < 65%
  - daily forced ventilation of the rooms (open window wide and short time)
  - elimination of contaminated wallpaper, furnishing and carpet
  - humid stonework -> repair if possible

C) Control by a site visit to determine independently that elimination of antigen was successful (Trial day 56 (49 - 63), at home)

If elimination was not successful: repeat consultation and education (issue 1. and 2.).

	Yes	No	Comment
Has the antigen identified above been eliminated successfully?	O	O	

4.2 Investigational treatments

4.2.1 General information about investigational medicinal product (IMP)

International nonproprietary name (INN): prednisolone
Formulation: hard capsules (capsules with tablets)
Manufacturer: Pharmacy University Medical Center Mainz

Comparative Product (Placebo)

Generic name: Placebo (capsules with placebo tablets)
Formulation: hard capsules
Manufacturer: Pharmacy department University Medical Center Mainz

4.2.2 Therapeutic effects

Prednisolone is a synthetic corticosteroid, which is mainly used as a non-specific anti-inflammatory and immunosuppressive drug. It modifies the body's immune response to diverse stimuli. As Prednisolone is an analogue of the hormone hydrocortisone it may cause dose – and time-dependent various metabolic effects. Prednisolone is indicated in the treatment of various conditions such as for example rheumatic diseases, chronic inflammatory bowel disease, allergic or hematological diseases. In pneumology it is used in asthma therapy as well as in many other pulmonary diseases, including interstitial lung diseases.

4.2.3 Known side effects

Side effects

Common adverse reactions for corticosteroids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioural and mood changes, increased appetite and weight gain.

Allergic Reactions: Anaphylactoid reaction, anaphylaxis, angioedema

Cardiovascular: Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

Dermatologic: Acne, allergic dermatitis, cutaneous and subcutaneous atrophy, dry scalp, edema, facial erythema, hyper or hypo-pigmentation, impaired wound healing, increased sweating, petechiae and ecchymoses, rash, sterile abscess, striae, suppressed reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria

Endocrine: Abnormal fat deposits, decreased carbohydrate tolerance, development of Cushingoid state, hirsutism, manifestations of latent diabetes mellitus and increased requirements for insulin or oral hypoglycemic agents in diabetics, menstrual irregularities, moon facies, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery or illness), suppression of growth in children

Fluid and Electrolyte Disturbances: Fluid retention, potassium loss, hypertension, hypokalemic alkalosis, sodium retention

Gastrointestinal: Abdominal distention, elevation in serum liver enzymes levels (usually reversible upon discontinuation), hepatomegaly hiccups, malaise, nausea, pancreatitis, peptic ulcer with possible perforation and and hemorrhage, ulcerative esophagitis

General: Increased appetite and weight gain

Metabolic: Negative nitrogen balance due to protein catabolism

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, charcot-like arthropathy, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures

Neurological: Arachnoiditis, convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually following discontinuation of treatment, insomnia, meningitis, mood swings, neuritis, neuropathy, paraparesis/paraplegia, paresthesia, personality changes, sensory disturbances, vertigo

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, and posterior subcapsular cataracts

Reproductive: Alteration in motility and number of spermatozoa

Drug interactions

- **Aminoglutethimide:** Aminoglutethimide may lead to loss of corticosteroid-induced adrenal suppression.
- **Amphotericin B:** There have been cases reported in which concomitant use of Amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see also **Potassium depleting agents**).
- **Anticholinesterase agents:** Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.
- **Anticoagulant agents:** Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.
- **Antidiabetic agents: Antidiabetic agents:** Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required**Antitubercular drugs:** Serum concentrations of isoniazid may be decreased.
- **CYP 3A4 inducers (e.g., barbiturates, phenytoin, carbamazepine, and rifampin):** Drugs such as barbiturates, phenytoin, ephedrine, and rifampin, which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage prednisolone be increased.
- **CYP 3A4 inhibitors (e.g., ketoconazole, macrolide antibiotics):** Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60% leading to an increased risk of corticosteroid side effects.
- **Cholestyramine:** Cholestyramine may increase the clearance of corticosteroids.
- **Cyclosporine:** Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with concurrent use.

- **Digitalis:** Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.
- **Estrogens, including oral contraceptives:** Estrogens may decrease the hepatic metabolism of certain corticosteroids thereby increasing their effect.
- **NSAIDs including aspirin and salicylates:** Concomitant use of aspirin or other non-steroidal anti-inflammatory agents and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.
- **Potassium depleting agents (e.g., diuretics, Amphotericin B):** When corticosteroids are administered concomitantly with potassium-depleting agents, patients should be observed closely for development of hypokalemia.
- **Skin tests:** Corticosteroids may suppress reactions to skin tests.
- **Toxoids and live or inactivated vaccines:** Due to inhibition of antibody response, patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines

Warnings and precautions

Alterations in Endocrine Function

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Drug induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Mineralocorticoid supplementation is of particular importance in infancy.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

With the doses suggested in this trial such alterations in endocrine function are not expected to occur.

Increased Risks Related to Infections

Corticosteroids may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic infections. The degree to which the dose, route and duration of corticosteroid administration correlates with the specific risks of infection is not well characterized, however, with increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Corticosteroids may mask some signs of infection and may reduce resistance to new infections.

Corticosteroids may exacerbate infections and increase risk of disseminated infection.

The use of prednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

Chickenpox and measles can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In children or adults who have not had these diseases, particular care should be taken to avoid exposure. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions.

Corticosteroids may increase risk of reactivation or exacerbation of latent infection.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhoea.

Corticosteroids should not be used in cerebral malaria.

Alterations in Cardiovascular/Renal Function

Corticosteroids can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium and calcium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. These agents should be used with caution in patients with hypertension, congestive heart failure, or renal insufficiency.

Literature reports suggest an association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with caution in these patients.

Use in Patients with Gastrointestinal Disorders

There is an increased risk of gastrointestinal perforation in patients with certain GI disorders. Signs of GI perforation, such as peritoneal irritation, may be masked in patients receiving corticosteroids.

Corticosteroids should be used with caution if there is a probability of impending perforation, abscess or other pyogenic infections; diverticulitis; fresh intestinal anastomoses; and active or latent peptic ulcer.

Behavioral and Mood Disturbances

Corticosteroid use may be associated with central nervous system effects ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Decrease in Bone Density

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy and bone density should be monitored in patients on long-term corticosteroid therapy.

Ophthalmic Effects

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Patients with Ocular Herpes Simplex

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

Vaccination

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered, however, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

Effect on Growth and Development

Long-term use of corticosteroids can have negative effects on growth and development in children. Growth and development of pediatric patients on prolonged corticosteroid therapy should be carefully monitored.

Use in Pregnancy

Prednisolone can cause fetal harm when administered to a pregnant woman. Human and animal studies suggest that use of corticosteroids during the first trimester of pregnancy is associated with an increased risk of orofacial clefts, intrauterine growth restriction and decreased birth weight. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the foetus.

Neuromuscular Effects

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Kaposi's Sarcoma

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

4.2.4 Dosage schedule

- Steroid pulse as short term common treatment for EAA, *not* used as trial medication; will be received by all subjects:
  methylprednisolone 10 mg/kg bw/d (max. 1g) i.v. over 1h for 3 days.
  Before starting the steroid pulse, serum levels for potassium have to be checked, if < 3,5 mmol/l substitute oral potassium during d1 through d3 of the pulse. If there are any signs of an acute intervening infection (e.g. fever, other organ involvement, e.g. urinary tract infection or otitis, etc) the steroid pulse must not be administered.

- Oral prednisolone as trial medication:
  Anticipated dose:
  first month after steroid pulse 0.5 mg/kg bw/d, second month 0.25 mg/kg bw/d, and third month 0.125 mg/kg bw/d in a single morning dose
  Individual capsules will be prepared using rounded dose (see 14. Appendix dosage table)

4.2.5 Overdose instructions

The effects of accidental ingestion of large quantities of prednisolone over a very short period of time have not been reported.

4.2.6 Treatment assignment

The trial medication will be administered only to subjects included in this trial.

Subjects withdrawn from the trial retain their identification codes (e.g. randomization number). New subjects will always receive a new identification code.

4.2.7 Treatment after the end of the trial

Treatment after the end of the trial is at the discretion of the investigator.

4.2.8 Packaging and labelling

The trial medication will be labelled according to local regulations.

The trial medication will be packed by pharmacy university medical centre Mainz.

Statements will be printed on the label(s) as required by local regulations.

4.2.9 Drug storage, supplies and accountability

The investigator will take inventory and acknowledge the receipt of all shipments of the trial medication. All trial medication must be kept in a locked area with access restricted to designated trial staff.

The trial medication must be dryly stored in accordance with manufacturer's instructions.

The investigator will also keep accurate records of the quantities of trial medication dispensed, used, and returned by each subject on the drug accountability form.

The site monitor will periodically check the supplies of trial medication held by the investigator to verify the correct accountability of all trial medication used. At the end of the trial, all unused trial medication and all medication containers will be completely returned to pharmacy Mainz in case no other procedure is agreed.

It will be assured that a final drug accountability report is prepared and maintained by the investigator.

4.2.10 Procedures for monitoring subject compliance

Trial medication will be dispensed to the subjects by the investigator.

Subjects will be instructed to bring all trial medication to the trial site at every visit (including all empty packages and unused trial medication), compliance will be assessed. Details will be recorded in the CRF and on the drug accountability form in the investigator site file.

4.2.11 Medication intake

Medication intake should take place with the meals or shortly after the meals. Whole capsules will be taken with liquid (50-100ml water, tea or apple juice).

4.3 Not permitted medication

The following concomitant treatments are not permitted during the trial:
Other systemic glucocorticosteroids as concomitant treatments are not permitted during the trial. However their usage as rescue therapy by the attending physician is possible and must be documented appropriately. Inhaled steroids are left unchanged if patient is currently on; if off, do not introduce them in the following 6 months.

For interactions with other medication and warnings please see 4.2.3.

4.4 Open rescue treatment if lung function does not improve

With removal of the allergen by hospitalization and cleaning of the home from offending allergenes which is usually done during the initial hospital stay, and after application of the 3d steroid boost to all subjects, a steady improvement in lung function is anticipated. This will be closely monitored by monthly lung function measurements in the first 3 months and at 6 months or additional visits at the discretion of the treating physician. FVC (% predicted) is expected to increase from visit to visit.

If this is not the case, continuing allergen exposure must be considered and a re-evaluation of the allergen elimination has to be performed.

If there is no appropriate improvement of lung function despite appropriate allergen elimination, an open rescue treatment with oral prednisolone (0.5 mg/kg bw/d) should be given till the patient's lung function improves. An alternative may be pulsed methylprednisolone (10 mg/kg bw/d). Extra visits at the discretion of the treating physician may be scheduled.

If the result of the oral prednisolone is not satisfying, re-evaluation of the diagnosis and possibly de-blinding of the study medication should be considered. Alternative medication, including steroid saving drugs may be considered.

All rescue treatments necessary will be recorded and the cumulative amount of steroids necessary used as a secondary outcome variable.

5. TRIAL SCHEDULE

Detailed trial schedule is given in table 1, page 7. All trial visits and measurements are part of the routine investigation and follow up of children with EAA, except the following:

Screening (Inpatient, day -21 to -2)
The following parameters have to be measured, data has to be collected and documented:

- Patient information and informed consent with the use of the consent form for each age group
- Inclusion/exclusion criteria have to be checked
  Randomization must occur directly after consent to the study is given, at least 1 week before the first dose of oral prednisolone; this is necessary to allow for preparation and shipping of the study medication.

Baseline (Inpatient, day -4 to -2)

- The patient or his parents should fill out the questionnaire for evaluation of Quality-of-life
- The patient or his parents should fill out the questionnaire for evaluation of health economics

Discharge (Inpatient, day 1)

- Trial medication will be provided to the patient

Personal contact (day 56 (35-74))
Expert allergen consultation and education at home with control, if the elimination of allergen has been successful

Telephone contact (day 126 (119, 133))

- Vital signs (Height, weight, RR, pulse, temperature), measured by the parents
- Documentation of adverse events

Visit 3 (day 84 (74-94)

- The patient or his parents should fill out the questionnaire for evaluation of Quality-of-life
- The patient or his parents should fill out the questionnaire for evaluation of health economics

Visit 4 (day 168 (148-188)

- The patient or his parents should fill out the questionnaire for evaluation of Quality-of-life
- The patient or his parents should fill out the questionnaire for evaluation of health economics
- End of trial (final visit)

Long term follow up (annually)

- The patient or his parents should fill out the questionnaire for evaluation of Health economics
- The patient or his parents should fill out the questionnaire for evaluation of Quality-of-life
- Build a cohort into adulthood

6. TRIAL METHODS

6.1 Assessment of efficacy

The primary analysis variable is the improvement in FVC (difference after 6 months and baseline). The 6 months and baseline FVC values will be given in percent deviation from the norm values tabulated by Quanjer PH., et al. 2013. FVC will be measured by performing a standardized spirometry with defined quality criteria according to the ATS/ERS guideline. Therefore a standard operation procedure will be provided.
For the evaluation of the quality of life a standardized questionnaire, the “PedsQL”, will be used.

6.2 Assessment of safety

6.2.1 Adverse events

6.2.1.1 *Definitions*

Adverse Event (AE)

According to GCP, an adverse event (AE) is defined as any untoward medical occurrence in a subject treated with a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- a new symptom or a new diagnosis
- a new medical condition or an accident
- a change in laboratory parameters
- an intercurrent illness or accident
- worsening of a medical condition/diseases existing before the start of the clinical trial
- recurrence of a disease
- an increase in frequency or intensity of episodic diseases.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present before inclusion in the trial. In the latter case the condition should be reported as medical history.

Change in laboratory parameters: The criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in trial dosing outside of protocol-stipulated dose adjustments, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.
- Progression of EAA under treatment should not be reported as an adverse event. However, if EAA leads to a fatal outcome during the trial or within the safety reporting period, then disease progression should be reported as an adverse event and as a serious adverse event with outcome “death”.

Serious adverse event (SAE)

A serious adverse event (SAE) is one that at any dose (including overdose):

- results in death
- is life-threatening[1]
- requires subject hospitalization or prolongation of existing hospitalization[2]
- results in persistent or significant disability/incapacity[3] or
- is a congenital anomaly/birth defect
- is an important medical event[4].

Comment:
Death is an outcome of an event. The event that resulted in death should be recorded and reported as an SAE.

[1]“Life-threatening” means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]If the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to start of the trial) or not associated with an adverse event (e.g., social hospitalisation for purpose) or results in a hospital stay less than 12 hours, the serious criterion “hospitalisation” is not fulfilled. However, it should be noted that invasive treatment during a hospitalisation may fulfil the criteria of “medically important” and may be reportable as a serious adverse event dependent on clinical judgement.

An inpatient rehabilitation program per se does not fulfil the seriousness criterion “hospitalization”. In this case the investigator should evaluate carefully whether the reason for the inpatient rehabilitation program has to be documented as an AE/SAE.

[3]“Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions. The irreversible injury of an organ function (e.g., paresis, diabetes, cardiac arrhythmia) fulfils this criterion.

[4]Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment should be considered as medically important.

Clarification of the onset and end date of AEs and SAEs

The onset date of the AE is defined as the onset of signs and symptoms or a change from baseline. The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious, i.e., met at least one of the ICH criteria for seriousness.

The end date of the AE is defined as the date when the symptoms resolve, or the event is considered stable. The end date of the SAE is defined as the time the seriousness criteria are no longer applicable.

The end date of the SAE must not be later than the end date of the corresponding AE.

AEs and SAEs that are on-going at the time of death are considered not resolved or resolving.

Clarification of the difference in meaning between "serious" and "severe":

The terms “serious” and “severe” are not synonymous but are often used interchangeably. The term ‘severe’ is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache). This is not the same as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.”

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is every SAE with an at least possible relationship to the investigational medicinal product which is unexpected.

An unexpected serious adverse reaction is any adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., the Investigator’s Brochure or the current SmPC).

6.2.1.2 *Assessment of AEs by investigator*

Subjects must be carefully monitored for adverse events by the investigator. The intensity of the adverse events and the causal relation to trial medication and/or procedures are to be assessed.

Intensity/Severity

The intensity of an AE will be assessed by the investigator as follows:

Mild: Temporary event which is tolerated well by the subject and does not interfere with normal daily activities.

Moderate: Event which results in discomfort for the subject and impairs his/her normal activity.

Severe: Event which results in substantial impairment of normal activities of subject.

If the event is serious, the severity reported in the adverse event must be consistent with the severity included in the adverse event report.

Causal relation to trial medication/procedures

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the documentation. Factors to be considered in assessing the relationship of the adverse event to study drug include:

• The temporal sequence from drug administration: The investigator has to consider, if the event occurred before first intake of study medication or long time after last intake. Additionally the length of time from drug exposure to event should be evaluated in the clinical context of the event.

• Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.

• Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

• Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

Positive causal relationship:

An assessment of 'related' implies a reasonable possibility of a causal relationship between the event and the investigational medicinal product (IMP).

This means that there are facts (evidence) or arguments to suggest a causal relationship, such as:

- A close temporal relationship
- A common drug reaction to the IMP
- No plausible alternative cause

Negative causal relationship:

An assessment of 'not related' means that there is no reasonable possibility of a causal relationship between the event and the investigational medicinal product.

This includes for example:

- Another cause of the adverse event is more plausible
- A temporal sequence cannot be established with the onset of the adverse event and administration of the study treatment
- A causal relationship is considered biologically implausible.

6.2.1.3 *Period of observation*

In this trial, the period of observation for collection of adverse events extends from first intake of study medication (day 0) up to visit 3 (final visit after 6 months).

If the investigator detects a serious adverse event in a trial subject after the end of the period of observation, and considers the event possibly related to the prior trial, he should contact the sponsor to determine how the adverse event should be documented and reported.

6.2.1.4 *Documentation of AEs and Follow up*

All AEs (whether serious or not) reported by the subject or detected by the investigator will be documented on the appropriate pages of the case report form (CRF). AEs must also be documented in the subject's medical records.
If the adverse event is serious (see Section 6.2.1.1), the investigator must complete, in addition to the "Adverse Event Page", a "Serious Adverse Event Form" at the time the serious adverse event is detected.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All subjects who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up, but no longer than 90 days after the end of the trial.

Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

6.2.1.5 *Immediate reporting of SAEs by investigator*

SAEs must immediately (within 24 hours of the investigator's awareness) be reported to:

IZKS Mainz
Langenbeckstr 2
55131 Mainz
FAX 0049 6131/17-9916

The initial SAE Report should be as complete as possible including the essential details of subject's identification (screening number, random number), the serious adverse event (medical term, diagnosis), the trial medication and the assessment of the causal relationship between the event and the trial medication. The SAE report must be reviewed and signed by the investigator.

The investigator should provide related additional information on the clinical course and the outcome of each SAE as soon as possible (Follow up report).

The "Serious Adverse Event Form" is provided in the Investigator Site File.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfils the definition of "serious adverse event", it must be reported as such.

6.2.1.6 *Immediate Reporting of pregnancy by investigator*

Any **pregnancy** diagnosed in a female subject during treatment with the investigational product must be reported immediately using the "Pregnancy Reporting Form" to:

IZKS Mainz
Langenbeckstr 2
55131 Mainz
FAX 0049 6131/17-9916

Pregnancy occuring during the clinical trial, although not considered a SAE, must be reported within the same timelines as a serious adverse event. The outcome of a pregnancy should be followed up carefully and abnormal outcome of mother or child should be reported if any.

6.2.1.7 *Documentation of Abuse, Misuse, Overdose and Medication Error*

All special events such as study medication abuse, misuse, overdose and medication errors including dilution errors and infusion rate errors have to be documented in the subject's CRF and source documents. If any abuse, misuse, overdose, or medication errors lead to an adverse event, then the event has to be documented and reported as AE/SAE.

6.2.2 Other safety data

Routine physical examination and laboratory determination as specified above at study visits.

6.2.2.1 *Safety evaluation and Reporting by sponsor*

The sponsor will ensure that all legal reporting requirements are met. According to GCP the sponsor is responsible for the continuous safety evaluation of the investigational product(s) and the clinical trial.
The sponsor Safety Management of IZKS Mainz on behalf of the sponsor will conduct the management of SAEs and the expedited reporting as required by German Drug Law (AMG) and GCP regulation (GCP-V). Suspected unexpected serious adverse reactions (SUSARs) and safety issues as defined by GCP-V are determined for expedited reporting: The competent authority and the ethics committees should be notified as soon as possible but not later than 15 calendar days if the event is non-fatal and 7 calendar days if it was fatal.
All investigators will be informed within the same timeframe.
The marketing authorization holder of the IMP should be informed.

Work flow and procedures concerning SAE management will be described in a separate document.

During the clinical trial the Safety Management of IZKS Mainz on behalf of the sponsor will submit the Development Safety Update Report (DSUR) including a list of all serious adverse reactions to the ethics committee(s), the competent authority (BfArM) and DMC once a year.

6.2.2.2 *Emergency procedures*

During and following a subject's participation in the trial, the investigator should ensure that adequate medical care is provided to a subject for any AEs including clinically significant laboratory values. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

<u>Emergency Unblinding:</u>

If it is medically imperative to know what trial medication the subject is receiving, the investigator or authorized person should open the sealed unblinding codes. The investigator or the person who

breaks the blind must record the date and the reasons for doing so in the CRF, in the subject's medical record and on the unblinding codes.

6.3 Other assessments

6.3.1 Prior and concomitant illnesses

Relevant additional illnesses present at the time of informed consent are regarded as concomitant illnesses and will be documented on the appropriate pages of the case report form (CRF).

6.3.2 Prior and concomitant treatments

Relevant additional treatments administered to the subjects on entry to the trial or at any time during the trial are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF.
For example in case of insufficient improvement of the symptoms, glucocorticoids may be administered to the subject and again searched for other sources of the allergen.

7. STATISTICS

Details of the statistical analysis of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP) that will be generated by IZKS Mainz and finalized before closing the data base and prior to breaking the blind. The SAP is based on the protocol including all amendments. The document may modify the plans outlined in this protocol; however any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. Any deviation from the original statistical plan must be described and justified in the final report. The statistical analysis will be conducted by means of SAS®.

7.1 Sample size

Power calculations were based on a one sided level of significance of alpha=0.05. Regulatory guidelines suggest the use of a two-sided level of significance. However, it is extremely improbable that in the time frame of the study the prednisolone arm will be significantly worse than the placebo arm. Power calculations were performed by means of a t-test with a correlation to the baseline value of 0.4. With 40 patients evaluable per protocol the study will have a power of 58% to detect non-inferiority of the placebo arm versus the prednisolone arm with a non-inferiority bound of 7%. The power calculations were done by SAS, Version 9.2.

7.2 Analysis populations

All subjects who signed informed consent / were assigned a randomization number are considered as enrolled/randomized subjects, even if they did not receive any trial treatment.

All subjects who received at least one dose of trial treatment and with at least one available post-baseline assessment of the primary analysis variable, will be included in the Intention-to-treat (ITT) population. This population is the primary analysis population. Within ITT population analyses subjects will be assigned to the treatment to which they were randomized.

The per protocol population are all subjects of the ITT population without any major protocol violation. This population is the primary analysis population.

The safety population comprises all subjects who received at least one dose of trial treatment. In analyses of the safety population subjects will be assigned to the treatment which they actually received.

The analysis populations will be defined prior to unblinding of the study.

7.3 Efficacy analyses

Efficacy:
The analyses will be specified more detailed in the statistical analysis plan (SAP). Descriptive statistics of qualitative data will consist of absolute and relative frequencies. For quantitative data the number of observations, mean, standard deviation, minimum and maximum will be presented.
The primary population for the analyses of efficacy is the randomized Population without major protocol violations.

7.3.1 Definition and analysis of primary endpoint

The primary analysis variable is the improvement in FVC (difference after 6 months and baseline). The 6 months and baseline FVC values will be given in percent deviation from the norm values tabulated by Quanjer PH., et al. 2013.
A difference between the changes in placebo and active treatment is considered not significant if FVC differences are < 7%. The working hypothesis of the study is that the placebo is not inferior to the prednisolone intervention.
The improvement in FVC will be compared between groups within an analysis of covariance (ANCOVA). Treatment will serve as a fixed factor and the baseline FVC value as a covariate. The primary analysis population will consist of all randomized patients without any major protocol violations. The two-sided 90% confidence interval for the treatment difference will be calculated. Sensitivity analyses will be performed by analyzing the same analysis model for all randomized patients. Additionally, the primary parameter will be analyzed by ANCOVA with additional terms for sex and height. Center effects will be explored by descriptive statistics. Missing values will not be replaced.
If appropriate, a Bayessian analysis with a suited prior distribution will be considered. This will be specified in the statistical analysis plan (SAP).

7.3.2 Analysis of secondary endpoints

All analysis of secondary endpoint will be interpreted purely exploratory. Descriptive statistics will be displayed for all

- Response according to the primary analysis variable: Each patient will be classified as a responder or non-responder. A patient is considered as a responder, if the FVC value after 6 months is more than or equal to 93% of the norm values tabulated by Quanjer PH., et al. 2013 and if the patient did not take any glucocorticoid rescue medication. Responders will be analysed by a Chi-Square Test.
- Forced Vital Capacity (FVC): Relative changes from Baseline after 3 months will be compared between groups by an analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline value as a covariate.
- Desaturation with standardized exercise test for children (O_2 saturation), Borg scale: Relative changes from Baseline after 3 months and 6 months will be compared between groups by an analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline value as a covariate.
- Quality-of-life (PedsQL): Descriptive statistics and exploratory p-values
- Health economics (EQ-5D): Health care costs and utility will be determined and combined with quality of life data. Afterwards they will be compared between treatment groups
- Weight for Height, Open usage of rescue glucocorticosteroids (mg/kg/6 months): Descriptive statistics and exploratory p-values only

7.3.3 Analysis of Subgroups

If appropriate, subgroups will be defined in the SAP.

7.3.4 Interim analyses

No interim analyses are planned.

7.4 Analysis of adverse events

All summaries and listings of safety data will be performed for the safety population.

Frequencies of subjects experiencing at least one adverse event (AE) will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include: A description of the event, duration, whether the AE was serious, intensity, relationship to trial drug, action taken, clinical outcome. Summary tables will present the number of subjects observed with AEs and corresponding percentages. Additional subcategories will be based on event intensity and relationship to trial drug.

A subject listing of all AEs will be prepared.

7.5 Analysis of clinical laboratory findings

Listings will be prepared for each laboratory measure and will be structured to permit review of the data per subject as they progress on treatment.

Summary tables will be prepared to examine the changes of laboratory measures over time. Additionally, shift tables will be provided to examine the changes of laboratory data from normal baseline to values outside the corresponding reference range during/after treatment.

8. QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Requirements for investigational sites and staff

The investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the trials treatments, and their trial-related duties and functions.

8.2 Direct entries

Data entries be entered in the CRF as Direct, are listed in the Monitor Manual in the section source data control.

8.3 Direct access to source data/documents

The investigator/institution must permit trial-related monitoring and auditing, as well as inspections by the appropriate competent authority and Ethics committees, providing direct access to source data/documents (Confidentiality see 10.3).

The subjects will be informed that representatives of the sponsor, independent ethics committee (IEC) or competent authority may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

8.4 Investigator site file and archiving

The investigator will be provided with an investigator site file (ISF) at the start of the trial. The investigator will archive all trial data and relevant correspondence in the ISF. The ISF, all source data and all documents will be kept filed according to the requirements of the ICH-GCP guidelines after termination of the trial.

After the end of the trial trial related documents e.g. trial master file (TMF) and CRFs will be stored in the archive of the sponsor.

It is the responsibility of the investigator to ensure that the subject-identification sheets are stored for at least 15 years beyond the end of the clinical trial. All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

8.5 Monitoring

Monitoring will be done by personal visits from a clinical monitor according to SOPs of the IZKS Mainz.
Each site will be visited by the monitor at regular intervals to ensure compliance with the trial protocol, GCP and legal aspects. The monitor will review the entries into the eCRF for completeness and correctness and verify the entries on the basis of the source documents.

The presence of correct informed consents will be checked for every subject.

Details will be specified in the monitoring manual for this trial.

The investigator must allow the monitor to look at all relevant documents and must provide support at all times to the monitor.

By frequent communications (letters, telephone, fax), the monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.

8.6 Inspection by authority and audits

Competent authority and by the sponsor authorised persons (auditor) may request access to all source documents, CRF, and other trial documentation in case of an inspection or audit. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities. Source data documents can be copied during inspection or audit in case the identity of the subject have been made unrecognizable.

8.7 Audits

No audits are planned for this trial.

9. DATA MANAGEMENT

The Central Information Office Marburg is responsible for data management. All data management activities will be done according to the current Standard Operating Procedures (SOPs) of Central Information Office Marburg.

For reports and analysis the EDC system provides data export functionality for data management. The data can be exported in SAS or SPSS format for reports and analysis.

9.1 Subject identification database (IDAT)

The IMBEI Mainz is responsible for programming the subject identification database (IDAT) and its hosting. This database contains names and addresses of the subjects and for each subject a unique subject ID. This subject ID is used for all documentation on eCRF and Data Clarification Forms (DCF).

9.2 Medical Database / eCRF (MDAT)

The Central Information Office Marburg is responsible for programming the eCRF (electronic Case Report Form) and hosting the medical database (MDAT). The eCRF will be designed in accordance to the clinical trial protocol.

As EDC system the secuTrial® system of the Central Information Office Marburg will be used. secuTrial® is an internet based system with connection to a rational ORACLE® database. The software serves as remote data entry system for pseudonymized medical data. It includes functions for data entry in electronic forms, for data view, analysis and export.

The software development was strictly proceeded in accordance to a standardized procedural model, meeting all ISPE GAMP4 requirements of software validation. secuTrial® is permanently audited to meet all requirements according to GCP, AMG, EMEA and FDA (21 CFR Part 11). It includes three different audit trail systems for medical data, user management and eCRF changes. Audit trail includes all changes made through the eCRF system within the database with additional login information and timestamp. This assures that any documentation and/or changes to database, user roles and medical items are traceable anytime. Changes or corrections can only be made by persons who have access to the system with user specific, role based access rights. Last audit was in May 2013.

Data management based on GCP refers to the activities defined to achieve safe routines to efficiently enter patient information into a database, avoiding errors. The data management routines include procedures for handling of CRF, database setup and management, data entry and verification, data validation, quality control (QC) of database, and documentation of the performed activities including information of discrepancies in the process.

Subjects' data are documented with the EDC (Electronic Data Capture) system directly by the sites via web browser and are transferred via SSL encryption to the central medical database (MDAT). The EDC system is 21 CFR Part 11 compliant and has an implemented audit trail.

9.3 Secure Hosting of the Medical database (MDAT)

The server-hardware of the Central Information Office Marburg is recently renewed in November 2012 to a currently up-to-date high-level processing power and storage system state. The server system is housed in a cage-in-cage-room in the High Security Data Center Itenos of the T-Systems AG, Nürnberg (20000-1 and ITIL certified). For the secure system administration the I-Motion GmbH, Fürth, is responsible (ISO-9001 and KV-Safenet certified). Server support is provided exclusively by high qualified and experienced personal.

The secure hosting concept includes the conception and implementation of the safety and security standard operating procedures, the professional audit of all formal processes of data security and the continuous support by competent personal.

Network traffic between the internet and the firewall systems, between the firewall systems and the application servers and between the application and the database servers is controlled by network based intrusion detection systems. All warnings and errors are logged in a separated database,

located in the seperated IT-center of the I-Motion GmbH, Fürth, permanently controlled and watched by internal implemented analysis tools.

The high availability of the medical research data is guaranteed by redundant hard disk systems (RAID) and a generation based data backup strategy.
All medical data on the database servers and all log files of the firewall systems are backuped daily. Exchange of the backup-tapes of the individual generations is weekly with a three-week rotation. Tapes of the last generation are stored in a banque safe-deposit box.

All systems are secured from power failures by a redundant uninterruptable emergency power supply system (USV, NEA).

The ASP-hosting and server connections (ISP-Connectivity) of the server farm, located in the T-Systems Data Center Itenos, Nürnberg, and their system administration by the I-Motion GmbH, Fürth, is audited regularly by the *Central Information Office Marburg*.
Audit is based on

- German National Institute of Security in Information Technology (BSI): Safeguard catalogues
- ISO 27000 (Management systems for Information Security)
- ISO 27001 (Information security management systems requirements specifications)
- ISO 27005 (Information security risk management)
- FDA Guidance for industry: Computerized Systems used in Clinical Trials (CSUCT)
- Good Clinical Data Management practices, ver. 4

Last audit was in June 2012.

9.4 Internet interface IDAT / MDAT

Medical database (MDAT) and Subject identification database (IDAT) use a SSL encrypted interface for communication. If the investigator of a site requests a “new patient” in the MDAT, the IDAT is asked to send a form to enter name and address. In the IDAT a unique subject ID is created and stored together with name and address.

The IDAT send the subject ID to the MDAT. (No identifying data will be sent back to and stored in the MDAT.) The MDAT will create a new database set for this subject ID and the medical data can be entered and stored.

If the investigator has forgotten the subject ID of his patient, he can use the “new patient” request to ask for an already existing subject ID. He can enter name and address, and the IDAT will send the according subject ID to the MDAT. The MDAT will open the dataset for this subject ID and additional medical data can be entered.

IDAT and MDAT databases are hosted at different independent locations, IDAT and MDAT databases are administrated from different independent teams.
The MDAT system administration does not have access to the Subject identification database (IDAT).
The IDAT system administration does not have access to the Medical database (MDAT).

9.5 Data entry

The investigator is responsible for the performance of the trial in accordance to the clinical trial protocol. All data collected during the trial have to be documented in the eCRF by authorized persons according to the personal log with delegation of authoritiy.

Detailed requirements for using the EDC system are specified in an EDC-Manual.

The eCRF should always reflect the latest observations on the patients participating in the study. Therefore, the eCRF are to be completed as soon as possible during or after the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all effect and safety evaluations. The investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off adverse and serious adverse event reports in the medical study database.

In order to use the EDC system all participants entering and monitoring data are provided with training materials and required documentation before start of the trial by IZKS Mainz. Every person using the EDC system has to complete a registration form (User-ID request) to confirm that they have received the training material and have been trained for data entry. For training of data entry a test/training database will be provided.

For support with data entry the Data management team of the national chILD-EU centers can be contacted. Each trial site has one responsible person who supports the national chILD-EU center in implementation of technical and organisational processes. A list of these persons is enclosed to DMP.

Users with monitoring function are not able to enter or change data. They have the possibility to view the data write protected (review function) and they can raise discrepancies and/or SDV marks in case of queries. Discrepancies which appear at data management are forwarded to the site directly.

9.6 Data concealment for electronic transfer

Every investigator, study nurse, monitor or other person involved in the trial receives her or his personal login data (username and password). Access rights to the database will depend on the group affiliation. Every person who gets access to the system has to fill in a registration form (User-ID request) and has to confirm that they have been adequately trained. Thus it is guaranteed that only authorized persons have access to the EDC system to document subjects in the trial.

9.7 Database quality control

Data have to be entered into the Medical database by the clinical investigator's staff, using single data entry with electronic verification.

The Medical database contains several completeness and plausibility data checks. During data entry these integrity checks help to minimize entry failures. They are programmed according to the data validation plan, signed by the coordinating investigator. Case report forms can only be stored after answer completeness and plausibility errors with correct data entries.

The data entry system allows the trial monitors to control the entry process with the help of several eCRF-internal review functions. Comments and requests can be processed by the trial site just in time. Subsequently, the entered data are systematically checked by the monitors, using the internal query system of the Medical database, completeness reports and printable queries details lists.

The investigator or a designated sub investigator, following review of the data in the eCRF, will confirm the validity of each subject's data by electronic signature. The EDC system is capable to make exact copies of data in legible paper form for inspections and audits.

Quality control audits of all key safety and efficacy data in the database are made prior to locking the database. Concomitant medications, medical history, current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the clinical trial, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked for additional data entries and final checks for plausibility, consistency and completeness of the data will be performed. Based on these checks, final queries can be produced. Any missing data or inconsistencies will be reported back to the respective site and clarified by the responsible investigator. A database audit will be accomplished to ensure and document the high-quality trial database. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

9.8 Storage and archiving of data

According to GCP, the investigator will archive all trial data (subject identification list, source data) and relevant correspondence in the Investigator Site File (ISF). The ISF, all source data and all documents itemized in section 8 of the ICH Consolidated Guideline on GCP will be archived after finalization of the trial according to the legal regulations.

Responsible for storage and archiving of other trial data will be the Coordinating investigator.

Storage and archiving of the electronic data during the trial will be assured by the Central Information Office Marburg. After completion of the trial all electronic data will be handed over to the sponsor.

10. ETHICAL AND LEGAL ASPECTS

10.1 Good clinical practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by good clinical practice (GCP) and the ethical principles described in the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

10.2 Patient information and informed consent

Before being admitted to the clinical trial, the subject or the representatives must consent to participate after being fully informed about the nature, scope, and possible consequences of the clinical trial.

The documents must be in a language understandable to the subject and must specify who informed the subject.

A copy of the signed informed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical trial until valid consent has been obtained.

If the subject has a primary physician the investigator should inform the subject's primary physician about the subject's participation in the trial and if the subject agrees to the primary physician being informed.

For subjects able to give informed consent:

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

For trials involving children:

Since the subjects in this trial are children, the consent of both legally authorized representatives must be sought. Children who are able to understand the nature, scope, and possible consequences of the clinical trial must also give their informed consent. The consent must be confirmed by the personally dated signature of the representatives (and child, if applicable) and the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the representatives. The original signed consent document will be retained by the investigator.

10.3 Confidentiality

The name of the subjects and other confidential information will not be supplied to the sponsor. During the clinical trial, subjects will be identified solely by means of an individual identification code (e.g. subject number, randomization number). Trial findings stored on a computer will be stored in accordance with local data protection laws and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of data legislation will be fulfilled in its entirety.
The subject will declare in the written consent to release the investigator from the medical professional secrecy to allow identification of subject's name and/or inspection of original data for monitoring purposes by health authority and authorized persons (monitors).

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

10.4 Responsibilities of investigator

The investigator will ensure that all persons assisting in the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.

The investigator will maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.
Any changes of the authorized trial personnel are to be communicated without delay to the IZKS Mainz.

10.5 Approval of trial protocol and substantial amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent ethics committee (IEC) for approval.

The documents will also be submitted to the competent authority (BfArM), in accordance with the respective local legal requirements.

Investigational products can only be supplied to the investigator after documentation on all ethical and legal requirements for starting the clinical trial has been received by the sponsor ("regulatory greenlight"). Before the first subject is enrolled in the trial, all ethical and legal requirements must be met.

The IEC and, if applicable, the competent authority must be informed of all subsequent protocol amendments, in accordance with the respective local legal requirements.

The sponsor must keep a record of all communications with the IEC and the competent authority.

The EC must be informed of the end of the trial in accordance with legal requirements.

10.6 Submission to local regulatory/competent authority

Before the start of trial, the sponsor is responsible for submission of all documents necessary to the competent authority for approval, in accordance to the respective local legal requirements.

10.7 Data monitoring committee (DMC)

Details concerning the DMC will be described in a separate document.

10.8 Insurance

According to legal requirements, the sponsor has subscribe to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The subject is responsible for notification. The insured person will be agreed to all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the subject.

Insurance provisions for this clinical trial are given in separate agreements.

10.9 Agreements

10.9.1 Financing of the trial

The trial is part of the EU research project "chILD EU".

The general conditions of financing for this trial are given in separate agreements.

10.9.2 Report

After conclusion of the trial, a report shall be written by the sponsor, in cooperation with the coordinating investigator. The report will include a statistical analysis and an appraisal of the results from a medical viewpoint. It will be based on the items listed in this trial protocol.

10.9.3 Publication policy

It is planned to publish the results of the trial as an original article in an appropriate medical journal as well as presentation at congresses. The Coordinating investigator is first author of the article and will present the data at the major congresses. The choice of the journal for the publication will be made by the coordinating investigator in agreement with the co-authors. Besides the Coordinating investigator, further authors of this article have to meet the following points:

- Recruitment of subjects into the study.
- Contribution to interpretation of the data.
- Contribution to drafting the article or revising it critically for important intellectual content.

All details regarding authorship are given in the Contract with Participants in the European chILD Registry (chILD-EU) Research Project, which was signed by each participant involved in the study

- Substantial contribution to the recruitment of subjects, i.e. one of the five best recruiting centers within the trial.
- Substantial contribution to interpretation of the data.
- Substantial contribution to drafting the article or revising it critically for important intellectual content.

11. SIGNATURES

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- The current risk-benefit assessment of the investigational medicinal product.
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP.

Coordinating Investigator

Prof. Dr. M. Griese

11/12/14
Date

Signature

Trial coordination

Dr. Kai Kronfeld

11.12.14
Date

Signature

Biometrician

Christian Ruckes, MSc

11.12.2014
Date

Christian Ruckes
Signature

12. DECLARATION OF INVESTIGATOR

I have read the above trial protocol and I confirm that it contains all information to accordingly conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enrol the first subject only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all subjects.

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described. I will provide a Curriculum Vitae (CV) before trial start. I agree that the CV may be submitted to the responsible competent authority.

I will conduct the trial in compliance with the protocol, GCP and the applicable regulatory requirements.

Investigator

Name
Address
Phone
Fax
e-Mail

_____ _____

Date Signature

Subinvestigator

Name
Address
Phone
Fax
e-Mail

_____ _____

Date Signature

13. REFERENCES

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14. APPENDIX DOSAGE TABLE

weight	month 1	month 2	month 3
(kg)	(mg Prednisolon)		
10	5	3	1
11	6	3	1
12	6	3	2
13	7	4	1
14	7	4	2
15	8	4	2
16	8	4	2
17	9	5	2
18	9	5	3
19	10	5	3
20	10	5	3
21	11	6	3
22	11	6	3
23	12	6	3
24	12	6	3
25	13	7	4
26	13	7	4
27	14	7	4
28	14	7	4
29	15	8	4
30	15	8	4
31	16	8	4
32	16	8	4
33	17	9	5
34	17	9	5
35	18	9	5
36	18	9	5
37	19	10	5
38	19	10	5
39	20	10	5
40	20	10	5
41	21	11	6
42	21	11	6
43	22	11	6
44	22	11	6
45	23	12	6
46	23	12	6
47	24	12	6

48	24	12	6
49	25	13	7
50	25	13	7
51	26	13	7
52	26	13	7
53	27	14	7
54	27	14	7
55	28	14	7
56	28	14	7
57	29	15	8
58	29	15	8
59	30	15	8
60	30	15	8
61	31	16	8
62	31	16	8
63	32	16	8
64	32	16	8
65	33	17	9
66	33	17	9
67	34	17	9
68	34	17	9
69	35	18	9
70	35	18	9
71	36	18	9
72	36	18	9
73	37	19	10
74	37	19	10
75	38	19	10
76	38	19	10
77	40	20	10
78	40	20	10
79	40	20	10
80	40	20	10
81	41	21	11
82	41	21	11
83	42	21	11
84	42	21	11
85	43	22	11
86	43	22	11
87	45	22	11
88	45	22	11
89	45	23	12

90	45	23	12
91	46	23	12
92	46	23	12
93	47	24	12
94	47	24	12
95	50	24	12
96	50	24	12
97	50	25	13
98	50	25	13
99	50	25	13
100	50	25	13