CLINICAL STUDY PROTOCOL

The **F**acial nerve palsy **A**nd **C**ortisone **E**valuation (**FACE**) study in children:

A randomized double-blind, placebo-controlled, multicenter trial

Development Phase

Sponsor Project No:	FACE-01
EudraCT number:	2017-004187-35
Investigational Product:	**Prednisolone**

Sponsor:	**Dalarnas county council** **(Landstinget Dalarna)**
Sponsor Representative:	**Lars Wallin, research manager (Forskningschef)** **Landstinget Dalarna** **Vasagatan 27** **791 37 Falun** **Sweden** **Telephone number: +46 (0)23 49 20 00** **E-mail address:** **lars.wallin@ltdalarna.se**
Coordinating Investigator	**Barbro Hedin Skogman, MD, PhD** **Center for Clinical Research Dalarna (CKF)** **Nissers väg 3** **S-791 82 Falun** **Sweden** **Telephone number +46 (0)23 49 20 00** **Mobile +46 (0)70 309 11 01** **E-mail address: barbro.hedinskogman@ltdalarna.se**

The clinical study will be conducted, and essential documentation archived, in compliance with the requirements of the ICH Guideline for Good Clinical Practice.

SYNOPSIS

Title of study:

The **F**acial nerve palsy **A**nd **C**ortisone **E**valuation (**FACE**) study in children: a randomized double-blind, placebo-controlled, multicenter trial

Name of Sponsor/Company:
Dalarnas county council (Landstinget Dalarna)

Name of investigational product:
Prednisolone

Investigator(s) and study center(s):

Barbro Hedin Skogman, coordinating investigator

9 study centers with a principal investigator at each center (see separate document "Ansvariga prövare")

Planned study period:	**Phase of development:**
2018-2022	Development Phase IV

Primary objective:

To evaluate the efficacy of cortisone versus placebo treatment in children with acute facial nerve palsy.

Secondary objective:

To evaluate the total recovery rate at 1 month as compared to the total recovery rate at 12 months, in order to evaluate if prediction of recovery at 1 month is feasible and/or useful in children with acute facial nerve palsy.

To evaluate subjective symptoms and influence in daily life in children with acute facial nerve palsy.

To evaluate the safety profile for cortisone in children with acute facial nerve palsy.

Methodology:
Randomized double-blind, placebo-controlled, multicenter trial

Number of subjects (planned):
500

Inclusion criteria:

1. 1-17 years of age
2. Acute peripheral unilateral facial nerve palsy
3. Less than 72 hours of duration of symptoms
4. Signed informed consent

SYNOPSIS

Exclusion criteria:

1. Head trauma < 1 month
2. Central or bilateral facial nerve palsy
3. Malformations in head and neck
4. Conditions not compatible with cortisone treatment (hypertension, diabetes mellitus, psychiatric disorder, active or latent tuberculosis, intolerance of lactose)
5. Current or past oncological diagnosis
6. Other serious medical conditions (meningitis, encephalitis, stroke)
7. Acute otitis media
8. Signs of herpes simplex or varicella zoster infection (vesicles in the ear region)
9. Pregnancy or breastfeeding
10. Use of any systemic or inhaled steroids within 2 weeks prior onset of symptoms
11. Immunization with live vaccine 1 month prior onset of symptoms
12. Requirement of live vaccine within 2 months from start of experimental treatment (prednisolone or placebo)
13. Evaluation of primary endpoint at 12 not feasible for any reason
14. Previously included into the FACE study

Investigational product, dosage and mode of administration:

Prednisolone tablets 5 mg, dosage 1 mg/kg body weight (maximum 50 mg) x 1, per oral

Duration of treatment:
10 days

Active control, dosage and mode of administration:
Placebo tablets, same number of tablets as investigational product for each child, maximum 10 tablets x 1, per oral

Primary Endpoint:

The total recovery rate at 12 months follow-up in the two treatment groups measured with the House-Brackmann scale.

Secondary Endpoints:

The total recovery rate at 12 months follow-up in the two treatment groups measured with the Sunnybrook scale.

The total recovery rate at 1 month follow-up as compared to the total recovery rate at 12 months follow-up, measured with Sunnybrook and House-Brackmann scale (prediction).

Quality of daily life at 1 and 12 months follow-up measured with the Facial Clinimetric Evaluation (FaCE) scale and the Facial Disability Index (FDI) and at the 12 months follow-up measured with the Synkinesis Assessment Questionnaire (SAQ).

Number of Adverse Events possibly or probably related to the study drug during the 12 months follow-up.

SYNOPSIS

Statistical methods:

Intention-to-treat will be applied when analyzing results from the primary outcome.

Comparisons between groups for dichotomous endpoints (recovery/no recovery) will be performed using Fisher's exact test and for categorical endpoints (scale) using Mann-Whitney U-test. For correlations between scales, Pearson's correlation test, or Cohen's kappa if appropriate, will be used.

When predicting recovery at 1 month to 12 months, diagnostic performance will be calculated on total recovery defined as House-Brackmann grade 1.

Analysis of early predictors will be performed to understand variance of subgroups. Furthermore, logistic regression analysis will be used to evaluate recovery in relation to baseline data.

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
CIOMS	Council for International Organisation of Medical Sciences
CKF	Center for Clinical Research, Dalarna
CRF	Case Report Form
CV	Curriculum vitae
DSUR	Development Safety Update Report
ENT	Ear Nose and Throat
ERB	Ethical Review Board
FACE	Facial nerve palsy and cortisone evaluation in children study
FaCE-scale	Facial Clinimetric Evaluation Scale
FDI	Facial Disability Index
GCP	Good Clinical Practice
ICF	Informed Consent Form
MPA	Medical Products Agency
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAQ	Synkinesis Assesment Questionnaire
SUSAR	Suspected Unexpected Serious Adverse Reaction

3 GENERAL INFORMATION/STUDY ADMINISTRATIVE STRUCTURE

Coordinating Investigator

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Also, see the form for the Regional Ethics Review Board in Uppsala, Bilaga 1and 9

4 SIGNATURE PAGES

SPONSOR

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Signature and date:

_____

Lars Wallin, Research manager
Dalarnas county council (Landstinget Dalarna)

COORDINATING INVESTIGATOR

I, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study.

I agree to conduct the study according to this protocol and according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable national laws and regulations.

Co-ordinating Investigator

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Signature and date:

_____

5 BACKGROUND INFORMATION

The annual incidence of acute facial nerve palsy in European pediatric populations are about 5-21/100 000 children (1,2). The facial nerve palsy is often idiopathic, but may be caused by a *Borrelia* infection in the nervous system (2,3). The physiological reason for impairment of the facial nerve is an anatomically tight passage through the bone of the scull and when the nerve becomes swollen, for some reason, the nerve function is impaired and the facial muscles on the ipsilateral side are affected.

In children, *Borrelia* associated facial nerve palsy occurs more often (65%) than *idiopathic* facial nerve palsy (35%) (2). *Borrelia* associated facial nerve palsy is treated with antibiotics according to European guidelines (4,5).

An acute facial nerve palsy, regardless of etiology, may lead to a permanent dysfunction in 20-30 % of the patients, involving problems with tear secretion, drooling and pronunciation in addition to cosmetic and social problems (6-8).

Adult patients with idiopathic acute facial nerve palsy (Bell's palsy) are recommended cortisone treatment in order to improve the recovery rate (9). This recommendation is based on several randomized clinical trials (RCTs) (9,10). Studies on pediatric patients with acute facial nerve palsy and cortisone treatment are scarce and no RCT has been performed (11,12).

There are a few uncontrolled treatment studies on cortisone to children with acute idiopathic facial nerve palsy showing a total recovery rate up to 80-90% (13-16). Prednisolone in a dosage of 1-2 mg/kg daily in 7-14 days has been used in pediatric patients without reported adverse events (15,17).

One protocol has recently been published from New Zealand about a RCT study using prednisolone 1 mg/kg daily in 10 days (with a reduced dose day 7-10) for treatment of children with facial nerve palsy (18). We have in the FACE study chosen prednisolone in a dosage of 1 mg/kg daily in 10 days without taper in order to give a treatment that is easy to follow (compliance) and effective enough to regain function of the facial nerve (efficacy).

5.1 STUDY RATIONALE

Since no RCT has previously been performed on cortisone treatment in children with acute facial nerve palsy, there is a lack of evidence-based guidelines.

The aim of the FACE study is to evaluate the efficacy and safety of cortisone treatment given to children with acute facial nerve palsy in a randomized placebo-controlled trial.

If the cortisone treatment is shown to be beneficial for recovery in children with facial nerve palsy, cortisone treatment will be introduced in clinical practice and international evidence-based guidelines will be published.

5.2 STUDY TIME TABLE

Study planning 2017-2018.

Patient inclusion and follow-up 2019-2022

Results and publishing 2022-2026

6 STUDY OBJECTIVES

6.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the efficacy of cortisone versus placebo treatment in children with acute facial nerve palsy.

6.2 SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the total recovery rate at 1 month as compared to the total recovery rate at 12 months, in order to evaluate if prediction of recovery at 1 month is feasible and/or useful in children with acute facial nerve palsy
- To evaluate subjective symptoms and influence in daily life in children with acute facial nerve palsy
- To evaluate the safety profile for cortisone in children with acute facial nerve palsy

7 ENDPOINTS

7.1 PRIMARY ENDPOINT

The primary endpoint is the total recovery rate at 12 months follow-up in the two treatment groups measured with the House-Brackmann scale (19).

The House-Brackmann scale (1 is normal function and 6 is total loss of function) is chosen as primary outcome measure since it is a validated, objective instrument, easy to perform and most frequently used in previous studies (13,14,19). The time point 12 months for evaluation of total recovery is chosen as no further improvement of the facial nerve function is expected after 12 months (14).

7.2 SECONDARY ENDPOINTS

Secondary endpoints are:

- the total recovery rate at 12 months follow-up in the two treatment groups measured with the Sunnybrook scale (20, 21).

  The Sunnybrook scale (100 is normal function and 0 is total loss of function) is another objective scale for grading the facial nerve function. It will be used as secondary outcome measure. It is validated for children, easy to perform and has been used in previous studies (20, 21). It correlates well to the House-Brackmann scale and has been shown to be useful for prediction of recovery in adult patients (21).

- the total recovery rate at 1 month follow-up as compared to the total recovery rate at 12 months follow-up, measured with Sunnybrook and House-Brackmann scale (prediction) (20, 21).

- quality of daily life at 1 and 12 months follow-up measured with the Facial Clinimetric Evaluation (FaCE) scale and the Facial Disability Index (FDI) and at the 12 months measured with the Synkinesis Assessment Questionnaire (SAQ) (22, 23).

- number of Adverse Events possibly or probably related to the study drug during the 12 months follow-up.

8 STUDY DESIGN

8.1 STUDY OUTLINE

The FACE study is a randomized double-blind, placebo-controlled, multicenter trial.

Efficacy of cortisone versus placebo treatment in children with acute facial nerve palsy will be measured by comparing the total recovery rate measured with the House-Brackmann scale at 12 months follow-up.

End of the first part of the study is defined as the 12 months follow-up visit for the last patient.

8.2 STUDY ASSESSMENTS AND PROCEDURES

A Principal Investigator (a pediatrician) at each study center will be responsible for clinical care of the patients.

The Principal Investigator (a pediatrician) or a co-Investigator (an Ear-Nose-Throat specialist) will be responsible for performing the objective evaluation of the facial nerve function on admission (or one day after) and at the follow-up visits 1 month and 12-months.

The Principal- and co-Investigators at each study center will be thoroughly informed how to assess the House-Brackmann and Sunnybrook scales in order to minimize inter-rater differences.

Study nurses will take care of parts of the study work, such as performing the one and two weeks telephone calls, collecting questionnaires from the child/parents/guardians, collecting and entering data in the CRFs and being the main contact person for the monitor.

Screening/Baseline visit

Children and their parents/guardians visiting the hospital for the child´s acute facial nerve palsy will be informed about the study and eligibility criteria will be checked. If the child and the parents/guardians accept to participate in the study, an informed consent (ICF) will be signed by both parents/guardians. If only one parent/guardian is present at the visit, the other parent/guardian will be contacted by telephone, informed about the study, given the chance to ask questions and sent an ICF by e-mail. The signed ICF will then be sent back by e-mail, or as a photocopy on the

mobile phone, to the investigator and saved in the Investigators file until the original ICF is returned.

Data about demographics, medical history, concomitant medication, physical examination including blood pressure will be collected. Blood sample for white and red blood cell count, CRP, electrolytes and glucose as well as investigation of the spinal fluid will be performed as part of normal clinical routine. The NeBoP score (a clinical neuroborreliosis prediction test), as used in routine, will be assessed on all children for early prediction of diagnosis associated to *Borrelia* infection (24).

Grading of the facial nerve palsy by using the House-Brackmann and Sunnybrook scales will be performed either by a pediatrician or an ear-nose-throat specialist (the principal or co-investigator).

The study medication including instructions about route of administration and dosage for the specific child will be distributed at the baseline visit. CRFs will be completed by the investigator or study nurse.

One week ±3 days telephone call and two weeks ±3 days telephone call

After one and two weeks, the study nurse will call the child and/or parents/guardians to follow up that study medication is taken according to instructions and to check whether any AEs have occurred. Bottles with remaining study medication will be returned after end of treatment for accountability check. Safety is followed-up by asking for AEs. CRFs will be completed by the study nurse.

One month ± 5 days and 12 months ±2 weeks follow-up visits

After 1 month and 12 months, the child with parents/guardians come to a follow-up at the pediatric or ENT-clinic. Grading of the facial nerve palsy with House-Brackmann and Sunnybrook will be performed. Safety followed-up by asking for adverse events. Also concomitant medications will be updated, if applicable. CRF's will be completed at 1 month and at 12 months by the investigator or study nurse.

The child and the parents/guardians will complete the Facial Clinimetric Evaluation (FaCE) scale, the Facial Disability Index (FDI) at 1 and 12 months follow-up and the Synkinesis Assessment Questionnaire (SAQ) at the 12 months follow-up.

Complementary treatment (for example physical therapy or massage) is asked for at the 12 months follow-up. If the patient has a moderate – severe persistent facial nerve palsy, a visit at an ENT-specialist will be arranged for further evaluation.

End of the study is defined as completed at the 12-months follow-up visit for the last included patient (LSLV). An end-of-the-study CRF for each participant will be completed by the Principal Investigator. The Medical Products Agency and the Regional Ethical Review Board will be informed within 90 days from the date of LSLV.

8.3 SCHEDULE OF EVENTS

	Screening/ Baseline	Telephone call 1 week ± 3 days	Telephone call 2 weeks ± 3 days	Visit 1 month ± 5 days	Visit 12 months ± 2 weeks
Informed consent	X				
Inclusion /Exclusion criteria	X				
Medical history	X				
Demographics	X				
Weight/length/BMI	X				
Physical examination	X				
NeBoP score	X				
House-Brackmann scale	X			X	X
Sunnybrook scale	X			X	X
Concomitant medication	X			X	X
Distribution of study medication	X				
Compliance of study medication		X	X		
Reporting of Adverse Events		X	X	X	X
Return of unused tablets				X	
Facial disability index				X	X
Facial Clinimetric Evaluation Scale				X	X
Synkinesis Assessment Questionnaire					X

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 SUBJECT INCLUSION CRITERIA

1. 1-17 years of age
2. Acute peripheral unilateral facial nerve palsy
3. Less than 72 hours since debut of symptoms
4. Signed informed consent

9.2 SUBJECT EXCLUSION CRITERIA

1. Head trauma < 1 month
2. Central or bilateral facial nerve palsy
3. Malformations in head and neck
4. Conditions not compatible with cortisone treatment (arterial hypertension, diabetes mellitus, psychiatric disorder, active or latent tuberculosis, intolerance of lactose)*
5. Current or past oncological diagnosis
6. Other serious medical conditions (meningitis, encephalitis, stroke)
7. Acute otitis media
8. Signs of herpes simplex or varicella zoster infection (vesicles in the ear region)
9. Pregnancy or breastfeeding
10. Use of any systemic or inhaled steroids within 2 weeks prior onset of symptoms
11. Immunization with live vaccine 1 month prior onset of symptoms
12. Requirement of live vaccine within 2 months from start of experimental treatment (prednisolone or placebo)
13. Evaluation of primary endpoint at 12 months not feasible for any reason
14. Previously included into the FACE study

*clarifications about some exclusion criterias:

Latent or active tuberculosis:
The Swedish children/adolescent population is at very low risk for TB.
However, immigrants, children to immigrants and adopted children may be of higher risk and these groups are in Sweden routinely tested at the health check-up, including PPD (and if possible PPD, a Quantiferon test and lung X-ray) in order to find children in risk of having latent or active TB. Children diagnosed with latent or active TB are treated according to Swedish guidelines and will be excluded for participation in the study. If negative Quantiferon test, the TB diagnosis is excluded and the child can participate in the study.

Arterial hypertension:
All children diagnosed with arterial hypertension (with or without treatment) will be excluded. All other eligible children will be checked for blood pressure according to normal procedures at pediatric emergency wards or pediatric out-patients clinics before inclusion in the study. If the blood pressure (measured after relaxation in 5-10 minutes, in the right arm with the correct size of the cuff and with a mean value of three measurements) is above the 90th percentile (for age, sex and length) the child will be excluded for participation (27).

Children not being eligible for enrolment will be registered on the screening list for gender, age and reason for exclusion.

9.3 WITHDRAWAL OF SUBJECTS

Participants can leave the study at any time without giving any specific reason but will be followed-up for safety reasons.

The Investigator can decide to withdraw a participants from a study treatment. If this decision is made because of a serious adverse event (SAE) related to the study medication, the treatment is discontinued and appropriate measures are taken. The participants will continue follow-up according to the protocol.

In case of written withdrawal of consent for follow-up visits and unless otherwise stated by the participants, the Investigator will be encouraged to follow the medical status of the patients.

The Sponsor should be notified immediately (within 24 hrs) about participants withdrawals due to Serious Adverse Events. The reason for the study discontinuation will be recorded in the CRF.

Specific criteria for withdrawal are:

- AE that precludes further continuation of treatment
- No compliance with study procedures
- The patient becomes pregnant
- Other medical reason according to the Investigator
- Patient's decision

Participants, who are withdrawn from the study will receive medical care according to local practice. In case of withdrawal due to an AE, participants will be closely monitored until resolution or stabilization of this AE. This may mean that follow-up will continue due to safety reasons.

Participants, who are not eligible for the study because in hindsight they were not eligible for the study, will continue to follow the study schedule.

For participants considered lost to follow-up, the CRF must be completed up to the last visit performed.

9.4 SUBJECT LOG AND SCREENING OF SUBJECTS

Participants will receive a consecutive screening number when signing the informed consent and are thereafter considered to be enrolled in the study.

It is the responsibility of the Investigator that all participants that have signed Informed Consent are listed on the "Screening and enrolment log". The reason for rejecting a participants before first treatment should be specified in the comment field of the log.

If the participant is eligible, he/she will receive a randomization number and the study drug bottle with the same randomization number will be distributed to the patient and the parents/guardians. It is the responsibility of the investigator to keep a patient identification log, identifying the individual behind each randomization number.

The Subject Enrolment and Identification log contains information to enable identification of each participant. It is included in the Investigator´s File and shall be kept by the Principal Investigator in a safe place.

The participants will have the same randomization number through the study and this number will not be reused in case the participant is withdrawn from the study.

10 TREATMENT OF SUBJECTS

10.1 TREATMENT ADMINISTRATION

The intervention is treatment with either prednisolone (T Prednisolone 5 mg), 1 mg/kg once daily in 10 days or control treatment (placebo) once daily in 10 days. The number of tablets is based on the child's weight pre-calculated in table 2. The dosage choice is based on results from earlier studies on prednisolone treatment, and a clear schedule (same dosage once daily in 10 days) will make a good compliance possible.

The specific child's dosage will be given to parents/guardians and noted in CRF. If the child has problems to swallow the tablets, the tablets may be crushed and mixed with a small amount (about one tablespoon) of something tasty in order to facilitate per oral administration and to ascertain the intake of the child's dosage of the study medication.

Table 2. Dosage of prednisolone/placebo. Treatment period is 10 days, maximum dosage is 50 mg per day.

Child´s weight /kg	Number of tablets/day	Total number of tablets
5 - 9.9	2	20
10 - 14,9	3	30
15 - 19.9	4	40
20 - 24.9	5	50
25 - 29.9	6	60
30 - 34.9	7	70
35 - 39.9	8	80
40 - 44.9	9	90
>45	10	100

10.2 DESCRIPTION OF INVESTIGATIONAL PRODUCTS

Tablet Prednisolon Alternova 5 mg (Orifarm Generics A/S), bottles of 100 tablets.
Batch 18A71, expire date 31-12-2020
Dosage 1 mg/kg (max 50 mg) once daily for 10 days
All bottles include 100 tablets.

Tablet Placebo (Orifarm Generics A/S), bottles of 100 tablets.
Batch 18A61, expire date 01-06-2021
Dosage 1 tablet/5 kg (max 10 tablets) once daily for 10 days.
All bottles include 100 tablets.

See separate product information from Medical Products Agency and the documentation of placebo.

10.3 PACKAGING AND LABELING OF INVESTIGATIONAL PRODUCTS

The study medication (prednisolone and placebo tablets) will be put in bottles, blinded and labeled by Tamro AB with a code according to randomization list (prepared by the statistician at UCR), sent to the central pharmacy then further distributed to the different study centers.
The study medication will be given to the patients/guardians at the screening/baseline visit after informed consent has been signed and eligibility for participation is confirmed by the Investigator.

10.4 STORAGE AND HANDLING

The study medication can be stored in room temperature. The medication can be placed at the local pharmacy or in a locked cabinet or room for medical products at the clinic.

10.5 RANDOMIZATION AND BLINDING

Randomization will be prepared by the study statistician. A randomization list using variable block sizes and stratification for study centers will be used and applied when undertaking blinding, coding and labeling the study medication (prednisolone or placebo).

The study drugs (prednisolone or placebo) will be labeled with the randomization code at Tamro AB and then sent to the central pharmacy for further distribution to the different study centers.

The codes for unblinding will be kept at the central pharmacy and at Center for Clinical Research (CKF) Dalarna. In case the code has to be broken due to an emergency situation, the Coordinating Investigator (Barbro Hedin Skogman) will be contacted, see details in section 12.8.

10.6 CONCOMITANT THERAPY

Children with *Borrelia* associated acute facial nerve palsy will receive antibiotic treatment according to national guidelines, i.e. ceftriaxone 50-100 mg/kg x 1 in 10-14 days (1-7 years of age), or doxycycline 4 mg/kg x 1 in 10-14 days, or 200 mg x 1 first day and then 100 mg x 1 in 10-14 days (5).

If other concomitant medications permitted in the study are taken, they will be listed in the CRF. Data registered are generic/trade name, dosage, start and end date of the medication, and indication.

Use of any systemic or inhaled steroids within 2 weeks prior to onset of symptoms is not permitted. No live vaccines are permitted during the period one month prior to onset until 2 months after study treatment. For more information about medical conditions not permitted in the study, see Subject Exclusion Criteria, section 9.2.

10.7 COMPLIANCE WITH THE TREATMENT

The study nurse will inform the child/parents on how to administer the study medication (small tablets with prednisolone or placebo). If it is not possible for the child to swallow the tablets, there is a possibility to crush and mix the tablets with something tasteful in order to facilitate compliance.

Telephone calls 1 and 2 weeks after baseline are planned to support the families and the compliance of the study medication and to follow-up if Adverse Events have occurred.

Parents/guardians will be instructed to return the packages with the remaining tablets for drug accountability check.

10.8 ACCOUNTABILITY OF INVESTIGATIONAL PRODUCTS

Accountability will be measured by counting remaining tablets in the packages, which should be returned to the study nurse at the pediatric clinic after usage, at the latest at the 1 month follow-up visit.

10.9 CONTINUATION OF TREATMENT

After 10 days treatment stops. No further treatment will replace the study medication.

Concomitant therapy (e.g. antibiotics 10-14 days, se 10.6) will be finished as prescribed by the responsible pediatrician.

11 ASSESSMENT OF EFFICACY

11.1 INVESTIGATOR'S ASSESSMENTS

The Investigators will perform evaluation using the House-Brackmann and Sunnybrook grading scales for facial nerve palsy at the three study visits (screening/baseline, 1 month, 12 months). Education for the study, including written instructions on how to perform the evaluation will be given to the investigators before study start.

11.2 SUBJECT´S ASSESSMENTS

The child and/or parents/guardians will complete the Facial Disability Index (FDI), the Facial Clinimetric Evaluation Scale (FaCE scale) at 1 month and 12 months follow-up and the Synkinesis Assessment Questionnaire (SAQ) at the 12 months follow-up to evaluate their personal subjective experience of the facial nerve palsy.

These questionnaires will be completed by the child/adolescent alone or together with the parents/guardians, which will be optional and documented at the end of each questionnaire.

12 ASSESSMENT OF SAFETY

Safety will be evaluated by recording of routine laboratory tests (white and red blood cells, CRP, electrolytes and glucose), physical examinations, blood pressure and vital signs measurements. Adverse Events (AEs) or Serious Adverse Events (SAEs), will be reported if occurring during the study period (12 months).

Any clinically relevant changes and actions taken, for instance occurrence of an adverse event or administration of concomitant medication, will be recorded in the CRF and hence in the database.

12.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence that does not necessarily have to have a causal relationship with the investigational product. An AE can be any unfavourable, unintended clinical sign, symptom, medical complaint or clinically relevant change in laboratory variables or clinical tests. Accidents, operations not pre-planned, changes in medication or deterioration in concurrent illness are also considered as AEs.

12.2 METHODS FOR ELICITING, RECORDING AND FOLLOW-UP OF ADVERSE EVENTS

Information regarding AEs is to be obtained by questioning or examining the subject after having signed the ICF. At each visit all new complaints and symptoms (i.e., those not existing prior to signing of informed consent) must be recorded on the AE CRF. Pre-existing complaints or symptoms that increase in intensity or frequency after having signed the ICF must also be reported as an AE.

All AEs must be characterized in terms of their start and stop dates, maximum intensity, action taken on the study medication, relationship to study medication, subject outcome and whether or not the AE led to a SAE. Any clinically relevant

increase or decrease to the intensity or frequency of a reported AE requires a separate entry on the AE form.

12.3 ASSESSMENT OF INTENSITY

The Investigator should rate the intensity of any AE as follows:
Mild: The AE does not interfere with the subject's usual function.
Moderate: The AE interferes to some extent with the subject's usual function.
Severe: The AE interferes significantly with the subject's usual function.

12.4 ASSESSMENT OF CAUSALITY

The Investigator shall judge whether or not, in his/her opinion, the AE is associated with the study medication. When stating the causality, the following nomenclature should be used:

Unrelated: There is little or no chance that the study medication caused the AE.
Possibly related: The association of the AE with the study medication is unknown, however, the AE is not clearly due to another condition.
Probably related: A reasonable temporal association exists between the AE and the study medication. Based on the Investigator's clinical experience, the association of the AE with the study treatment seems likely.

12.5 DEFINITION OF SERIOUS ADVERSE EVENTS

A serious AE is any untoward medical occurrence that at any dose:
- Results in death.
- If life threatening at the time of the event.
- Requires inpatient hospitalisation
- Requires prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These also should usually be considered serious.

Also serious events which could be associated with the study procedures (rather than with the study medication) will be reported as SAEs, even if occurring outside the treatment period.

Under this protocol, the following events will not be considered as an SAE and should not be entered on the SAE form:

Elective hospital admission
Pre-planned hospitalizations for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of a clinical study. These pre-planned hospitalizations and the underlying conditions must be entered on the medical history form.

12.6 REPORTING OF SAEs, SUSARs and DSUR

The reporting by the Investigator to the Sponsor shall cover all SAEs (whether or not considered as related to the study treatment), including their intensity and cause. The initial report should be sent within 24 h after becoming aware of the occurrence of the event, using a Serious Adverse Event Report Form. The SAE report forms must be sent via e-mail to the Sponsor (see contact details below). If additional information is required, a follow-up report should be sent as soon as possible within another 4 days.

Sponsor: Barbro Hedin Skogman	E-mail:barbro.hedinskogman@ltdalarna.se

If the initial SAE report is incomplete it should as far as possible be supplemented by detailed information on diagnosis/symptoms, the relationship with the start of treatment and the latest dose taken and any further relevant data.

The Investigator should also inform the Sponsor about other safety problems such as:
- Increased incidence and/or severity of AEs possibly or probably related to the study medication

If a participant discontinued the study because of an in-treatment SAE, this should be noted:
- On the SAE form by marking “dosing stopped” under “action taken”
- On the last visit CRF by marking “(serious) adverse event” as the reason for discontinuation

Suspected, Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life threatening shall be reported to the MPA and the ERB as soon as possible and at the latest within 7 calendar days from the first knowledge by the Sponsor. The report shall as far as possible be supplemented by additional information, but at the latest within a further 8 calendar days. It is the responsibility by the sponsor to report SUSAR to the MPA and ERB.

The reporting of other SUSARs to the MPA ad ERB shall be done as soon as possible, but not later than 15 calendar days after the first knowledge by the sponsor.

CIOMS forms will be used for submission to MPA, who will be responsible for the electronic reporting into EudraVigilance.

Sponsor should once a year during the study report safety issues including SAEs to the MPA and ERB by a Development Safety Update Report (DSUR).

12.7 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All (S)AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

12.8 PROCEDURES IN CASE OF MEDICAL EMERGENCY

The Investigator should ensure that there are procedures and expertise available at the study center to cope with emergencies during the study. The Coordinating Investigator must be informed when a code has been broken.

Code envelopes will be distributed to the centers in conjunction with distribution of the study drug. The envelopes will be stored at the clinic in case codes need to be broken for safety reasons.

There is also a possibility to contact the coordinating center where the complete code list will be stored. The persons listed have access to the code list, only one of them needs to be contacted:

Barbro Hedin Skogman, MD, PhD (co-ordinating Investigator)
Center for Clinical Research (CKF) Dalarna
Nissers väg 3
S-791 82 Falun, Sweden
Telephone number: +46 (0)23 49 20 00
Mobile: +46 (0)70 309 11 01
E-mail: barbro.hedinskogman@ltdalarna.se

or

Sofia Karlsson, MD, PhD-student (co-investigator)
Center for Clinical Research (CKF) Dalarna
Nissers väg 3
S-791 82 Falun, Sweden
Telephone number +46 (0)23 49 20 00
Mobile: +46 (0)70 351 92 82
E-mail address: sofia.a.karlsson@ltdalarna.se

or

Karin Björling (administrative staff)
Center for Clinical Research (CKF) Dalarna
Nissers väg 3
S-791 82 Falun, Sweden
Telephone number: +46 (0)720 835 921
E-mail: karin.bjorling@ltdalarna.se

or

Cecilia Lundgren (administrative staff)
Center for Clinical Research (CKF) Dalarna
Nissers väg 3
S-791 82 Falun, Sweden
Telephone number: +46 (0)720 833 835
E-mail: cecilia.lundgren@ltdalarna.se

At least one of these persons will always be available during the whole study period.

12.9 LABORATORY ASSESSMENTS

Safety laboratory assessments (white and red blood cells, CRP, electrolytes and glucose) will be performed at admission according to clinical practice. However, no laboratory data will be collected in the study.

13 STATISTICS AND DATA MANAGEMENT

13.1 DATA MANAGEMENT

All data collected in this study will be recorded in CRFs. Data will be entered by the Investigators and/or their delegated staff. Data captured via the CRF will be entered into a database at Center for Clinical Research Dalarna. A copy of each CRF will be retained at the study centre for at least 10 years following completion of the study depending on the applicable regulations.

Prior to the start of the clinical study the Investigator will complete a Signature and Delegation Log showing the names of persons who are authorized to enter or change data in the CRFs.

Signing end of the study is considered to be the final authorization of the CRF; it must be signed and dated by one of the Investigators. The signature is a guarantee that (s)he has reviewed the CRF and certifies them to be complete and accurate.

Monitoring by a Sponsor's representative will be performed to ensure the safety of the human subjects, the quality of data, its scientific integrity and compliance with the applicable guidelines and regulations. Both representatives of the Sponsor and relevant authorities must have access to all study data and documents at the clinic at any time.

The Sponsor will not collect data of subjects who are not randomised into the study (i.e. screening failures). All subjects asked to participate will be listed on a screening list, which will be filed in the Investigator Study File, and if a subject is not randomized, the reason for that has to be registered on the list. A copy of the screening list will be collected by the Sponsor.

Children not being eligible for enrolment will be registered on the screening list for gender, age and reason for exclusion.

13.2 STATISTICAL ANALYSIS

The statistical methods will be described in detail in a statistical analysis plan (SAP) that will be finalized and approved before data base lock is performed. Statistical testing may be undertaken for hypothesis generating purposes, using two-sided tests and 5% alpha level, unless otherwise stated.

Data will be presented by treatment group (prednisolone/placebo). Graphical methods may be used wherever it is regarded as appropriate.

The last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline. All data obtained on the CRF and entered into the database will be provided in separate data listings showing individual subject values. Tabulations of summary statistics, graphical presentations, and listings will be performed by the UCR statistician. All statistical calculations will be performed using SAS® version 9.4 or later (SAS Institute Inc., Cary, NC, USA) or SPSS statistics, version 21 (IBM Corporation, USA).

Intention-to-treat will be applied when analyzing results from the primary outcome. Comparisons between groups for dichotomous endpoints (recovery/no recovery)

will be performed using Fisher's exact test and for categorical endpoints (scale) using Mann-Whitney U-test. For correlations between scales, Pearson's correlation test, or Cohen's kappa if appropriate, will be used. When predicting recovery at 1 month to 12 months, diagnostic performance will be calculated on recovery defined as House-Brackmann grade 1. Analysis of early predictors will be performed to understand variance of subgroups. Furthermore, logistic regression analysis will be used to evaluate recovery in relation to baseline data.

Study patients that have been screened but not received any study medication, will be considered as screen failures and will not be included in the study database.

13.3 DETERMINATION OF SAMPLE SIZE

Power for the FACE study is calculated on the primary end-point (number of patients with total recovery from the facial nerve palsy in each intervention group, measured by House-Brackmann grade 1 at 12 months follow-up). A difference of 10% of the total recovery rate between groups (90% versus 80%) is estimated from earlier non-RCT treatment studies (3, 15) and used for calculations of sample size. A p-value less than 0.05, a power of 0.80 and a calculated portion of patients not taking part of the study follow-up is included in the analysis.

A sample size of 500 patients need to be included in the FACE study according to this power analysis. No minimum number of included patients at one single site is determined.

14 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigators/institutions will permit study-related monitoring, audits, review and regulatory inspections, providing access to source data/hospital records. Sponsor verifies that each patient has consented in writing to direct access to the original source data/hospital records by the use of written patient information and signed Informed Consent.

15 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 SOURCE DATA

The following minimum amount of information should be recorded in the hospital records:

Study

- Study title
- Aim of the study
- Randomization number
- Subject identification
- Date when signed Informed Consent was obtained
- Diagnosis
- Fulfillment of eligibility criteria
- Visit dates
- Concomitant medications
- Any AEs
- Specification of the subject's cessation in the study
- Specification of the subject's outcome in the study
- Specification of study treatment (after code break at study end)

Gradings by House-Brackmann and Sunnybrook, as well as information about Facial Clinimetric Evaluation Scale, Facial Disability Index and Synkinesis Assessment Questionnaire will be reported directly in the CRF as source data.

15.2 MONITORING

In accordance with the principles of Good Clinical Practice (GCP), monitoring of the study will be arranged by the Sponsor. During the study, the Monitor will have regular contacts with the study centers, including visits to ensure that the study is conducted and documented properly in compliance with the protocol, GCP and applicable regulatory requirements.

The study nurse will that ensure that accountability of study medication is performed and documented in an accountability log. The monitor will review source documents for verification of consistency with the data recorded in the CRFs. The Monitor will also provide information and support to the Investigator(s). The monitoring work is described in a monitoring plan.

The study center may also be subject to quality assurance audit by the Sponsor as well as inspection by the MPA. The Investigator and other responsible personnel

must be available during the monitoring visits, audits and inspections and should devote sufficient time to these processes.

The Investigator and study staff should provide a curriculum vitae (CV) or equivalent documentation of suitability to be responsible for the study. All Investigators and other responsible personnel should be listed together with their function in the study on the signature and delegation list.

15.3 DATA SAFETY MONITORING BOARD

An independent data safety monitoring board (DSMB) will be engaged, including 2-3 members. These member(s) will be chosen from having appropriate scientific knowledge in the field.

The DSMB will evaluate safety data after the first 50 patients have completed the study. The next safety evaluations will occur when 200 and 400 patients have been included. There is always a possibility to have more safety evaluations if found needed. A DSMB charter will be written for the members to outline the working procedures and their duties.

16 ETHICS REVIEW BOARD

It is the responsibility of the Sponsor to obtain approval of the study protocol/protocol amendments, the patient information and the Informed Consent from the ERB before enrolment of any subject into the study.

The study medication will not be delivered to the study centers until approval from the ERB has been obtained.

The Sponsor shall report all SUSARs also to the ERB, unless otherwise agreed. If a study stops prematurely at a study center for any reason, the ERB must be informed. At the end of the study, the Sponsor should notify the ERB. The Sponsor should file all correspondence with the ERB.

16.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the protocol, applicable regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions (Appendix 23.1).

16.2 RISK - BENEFITS

A risk analysis for this study has been made. These risks together with the actions to minimize these risks are compiled below:

	Anticipated risk	Action
1	Side effects such as minor behavior problems (mood changes), sleep disturbances, nausea or vomiting	Reported as Adverse Events and follow up until recovered. A Development Safety Update Report (DSUR) will be presented yearly to MPA
2	Trauma for the child to take medicine	Tablets may be crushed and mixed with something tasty. The study nurse will instruct the parents/guardians when study medication is distributed and will also follow up how it works by telephone calls one and two weeks after Baseline
3	No effect on the recovery rate	There is no alternative treatment, why there is no risk that the patient looses an effective treatment by participating in the study

A short-course oral treatment with corticosteroids (defined as 1-2 mg/kg once daily in 7-14 days) is not associated with major side effects, such as risk of growth retardation, osteoporosis or diabetes mellitus in children, but may be associated with minor side effects, such as behavioral problems (mood changes), sleeping disturbances, nauseas or vomiting in 4,3 – 5,4 % of cases (17,25,26).

The risk of minor side effects will be reduced with the dose 1 mg/kg x 1 (17), as we plan on using in the present study.

Increased susceptibility to infection (<1%) is the most frequent (S)AEs associated with short courses of corticosteroids (25,26). In five large RCTs on short-course corticosteroid treatment, three children with varicella infection needed intensive care due to complications (25).

Parents/guardians will be informed before start of treatment in the current study about the importance to attend health care if fever or signs of infection occur during the study period.

In summary, the benefits, i.e. possibly improved recovery of the facial nerve palsy are anticipated being higher than the risks.

16.3 PATIENT INFORMATION AND INFORMED CONSENT

It is the responsibility of the Investigator to provide each participant with full and adequate verbal and written information about the objectives, procedures and possible risks and benefits of the study. All participant will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether or not to participate in the study. All information about the study will be age-adjusted in order to obtain good adherence for both younger and older children and adolescents.

The written patient information must not be changed without being approved by the Ethics Review Board.

The participant will be notified of their voluntary participation and of their freedom to withdraw from the study at any time and without giving any particular reason. participant must also be informed that withdrawing from the study will not affect their future medical care, treatment or benefits to which the participant is otherwise entitled.

Parents/guardians will sign the informed consent for children 1-17 years of age.

The Investigator is responsible for obtaining written Informed Consent from all parents/guardians prior to enrolment in the study. If only one parent/guardian is present at the visit, the other parent/guardian will be contacted by telephone, informed about the study, given the chance to ask questions and sent an ICF by e-mail. The signed ICF will then be sent back by e-mail, or as a photocopy on the mobile phone, to the Investigator and saved in the Investigator's file until the original ICF is returned.

The parents/guardians will consent to:
- Participating in the study.
- Personnel from the sponsor or the regulatory authorities to gain full access to hospital records to check the quality of data collected in the study.
- Recording, collection and processing of data and storing of data in a database.
- Possible transfer of information from the study to countries outside the European Union (EU).

It should be clearly stated that the data will not identify any participant taking part in the study, in accordance with the European General Data Protection Regulation (GDPR) (2016/679/EU).

A copy of the patient information and the ICF will be given to the parents/guardians. The Investigator (or a co-Investigator) who gave the verbal and written information to the participant will sign the ICF. The Investigator will file the signed ICFs in the Investigator's File.

17 DATA HANDLING AND RECORD KEEPING

17.1 CASE REPORT FORMS

CRFs are required and should be completed for each included participant. The child's identity must always remain confidential.

Paper CRFs will be used and study data will be entered in a database at the Sponsor (Center for Clinical Research Dalarna). The completed study database is the sole property of the Sponsor and will not be made available in any form to third parties (except for authorized representatives of appropriate regulatory authorities) without written permission from the Sponsor.

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the CRF. Corrections to the CRF must be signed by the Investigator or a designated representative.

17.2 RECORD KEEPING

To enable audits and inspections by regulatory authorities, the Investigators will keep records (essential documents) of the study for at least 10 years. This includes any original source data related to the study, the subjects identification list (with subject numbers, full names and personal numbers), the original signed ICFs, copies of all CRFs and detailed records of study medication disposition.

The Sponsor is also, as per GCP-requirements, responsible for archiving their part of the study documentation.

18 INSURANCE

Patients participating in this study are covered by the Swedish Patient Insurance (Patientskadeförsäkringen LÖF-Landstingens Ömsesidiga Försäkringsbolag) and the Swedish Pharmaceutical Insurance (Läkemedelsförsäkringen).

19 PUBLICATION POLICY

All information not previously published concerning the clinical study is considered as confidential and will remain the sole property of the Sponsor. The Investigator agrees to use this information only in connection with this study and will not use it for other purposes without written permission from the Sponsor.

After completion of the study, the statistical analyses will be performed and the results will be presented to the Investigators. Based on these data, the Sponsor, in cooperation with the Investigators, will prepare a clinical study report. The report will be submitted to the MPA and may form the basis for a manuscript intended for publication in a medical/scientific journal.

20 SUPPLEMENTS

20.1 CHANGES OF THE STUDY PROTOCOL

No change in the study procedures will be effected without the mutual agreement of the Investigators and the Sponsor (except where necessary to eliminate an immediate hazard to subjects). All changes of the final study protocol must be documented by signed protocol amendments. If substantial changes to the design of the study are made, the MPA and the ERB will be notified for review and approval.

20.2 APPLICATION TO REGULATORY AUTHORITIES

Prior to initiating the clinical study, the Sponsor will submit an application for authorization to conduct the study, including all required documents, to the MPA. Additional documentation may be demanded for investigational products with special characteristics.

One complete application will be submitted. For each planned study center, the address and the name and position of the Investigator will be indicated on the application.

20.3 STAFF INFORMATION

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

20.4 CRITERIA FOR TERMINATION OF THE STUDY

The Sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects, but intends to exercise this right only for valid scientific or administrative reasons. After such a decision, all delivered unused investigational products and other study-related materials must be collected and all CRFs must be completed as far as possible.

The study can be prematurely discontinued in the following cases (examples):

- Unexpectedly high proportion of adverse events, possibly or probably related to the study medication.
- New findings about the investigational product(s) that changes the benefit/risk ratio.
- Study protocol is difficult to cope with.
- Recruitment of eligible subjects is far too low.
- Problems with manufacturing or stability of the investigational product(s).
- Unacceptable low Investigator, Sponsor or subject compliance.
- Critical change in personnel, administrative or scientific standards at the Sponsor or at the study centers.
- No significant result will be obtained as anticipated.

21 REFERENCES

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22 SIGNED AGREEMENT OF THE STUDY PROTOCOL

To be signed per study centre.

EudraCT number: 2017-004187-35

Title of the study:

The Facial nerve palsy And Cortisone Evaluation (FACE) study in children:
A randomized double-blind, placebo-controlled, multicenter trial

I, the undersigned, have read and understand the protocol specified above and agree on the contents. The study protocol, the Clinical Study Agreement and the additional information given about the study medication will serve as a basis for co-operation in this study.

I agree to conduct the study according to this protocol and according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable national laws and regulations.

PRINCIPAL INVESTIGATOR

Principal Investigator Address to participating clinic

Signature and date: _____

23 APPENDICES

23.1 DECLARATION OF HELSINKI

23.2 RATING SCALES OR DIARIES FOR ASSESSMENT OF EFFICACY OR SAFETY

23.3 LABELING OF INVESTIGATIONAL PRODUCTS