A Double-blind, Placebo-controlled Randomized Study Comparing the Effectiveness of a Single Dose of Betamethasone vs Placebo in Children with Symptomatic Adenovirus Infection.

Study protocol

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Acronyms cited in the study

GABHS	Group A beta-hemolytic streptococcus
BD	Body Temperature
ESR	Erythrocyte sedimentation rate
CRP	C-reactive Protein
SCP	Summary Characteristics Product
CRF	Case Report Form
GCP	Good Clinical Practice
CTCAE	Common Terminology Criteria for Adverse Events
NCI	National Cancer Institute
SAE	Serious Adverse Event
AE	Adverse Event
AR	Adverse Reaction
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reactions

Background and rational

Human adenoviruses can cause infections at any age, but are more common in the paediatric population, especially in children aged 3-5 years[1].

Among adenovirus diseases, pharyngitis, often accompanied by conjunctivitis, and pharyngeal-conjunctival fever,conjunctivitis are very common.[2]

Pharyngitis alone can mimic streptococcal infection. The illness is highly febrile and tends to last up to 5-7 days if treated with antipyretics alone.[3]

Adenovirus pharyngitis is characterised by a specific clinical and laboratory picture:

1) tonsillar hyperemia-hypertrophy, often with grey exudate, transparent.
2) visible involvement of the lymph nodes of the neck with laterocervical lymphadenopathy;
3) conjunctivitis (not always present).
4) neutrophilia (neutrophils >10,000/mmc), platelet (platelets >350,000/mmc), increased erythrocyte rate (ESR > 50/mmc) and C-reactive Protein (CRP > 5 mg/dl).
5) negativity of the pharyngeal buffer for Group A beta-hemolytic streptococcus (GABHS).

There are currently no effective treatments for this infection based on experimental studies. The use of betamethasone in mono-administration is considered effective in significantly reducing the hyper-inflammation that the virus can cause in paediatric patients. Nevertheless, it is an empirical therapeutic practise that is variably used, as the positive clinical experience favours its prescription, but due to a lack of experimental evidence. A retrospective observational study conducted by the University of Trieste[4] on 23 children hospitalised for tonsillitis concluded that mono-administration of betamethasone 0.1 mg/kg was followed by an almost immediate release within an interval of no more than 12 hours. This observation suggests that the adenoviral infection is not the cause of the protracted febrile syndrome, while the hyperinflammatory response triggered by the immune system appears to be the actual cause of the important symptomatology. This hyperinflammatory response can be eliminated by a single administration of betamethasone.[4]

This study aims to demonstrate that the timely use of betamethasone 0.1 mg/kg in a febrile infant with an adenoviral infection would prevent protracted symptomatology (reduction in fever duration, reduction in pharyngology, rapid resumption of feeding), thereby reducing hospitalisation and the need for intravenous rehydration/parenteral nutrition.

Betamethasone is a synthetic adrenocortical hormone derived from hydrocortisone. Its anti-inflammatory effect is manifested in the inhibition of capillary dilation, the migration of leukocytes and phagocytic activity. Specifically, it forms a complex in the cell with a glycoprotein that alters gene expression by determining the production of various enzymes and proteins, such as vasocortin and lipocortina. The latter acts by blocking the enzyme phospholipase A2, which leads to an inhibition of the release of arachidonic acid and a reduction in the synthesis of inflammatory mediators such as prostaglandins, leukotrienes and prostaciclinins.[5]

Numerous studies indicate that paediatric corticosteroids used over a short period of time are not associated with an increase in side effects. Therefore, their use in the single administration of a viral infection with adenovirus is safe in terms of side effects and may be associated with an improvement in the overall clinical condition of patients.

Objectives

The primary objective is to evaluate the efficacy of the mono-administration of betamethasone in children with adenoviral febrile infection in terms of increasing the proportion of children free of fever within 24 hours of administration.

Secondary objectives include reduction of pharyngeal tonsil pain, the incidence , frequency and duration of hospitalisation, time required for discharge and overall duration of fever.

Trial design

The Adeno-beta study is designed as a randomized double-blind clinical trial with placebo control. (experimental treatment vs placebo)

We adopted the double blind design since knowledge of the allocation arm could affect:

- the recording of both the primary outcome and the secondary outcomes (e.g. pain scale) carried out by parents
- therapeutic decisions (e.g. patient hospitalization) by the physicians.

Since, to our knowledge, there are no effective treatments for adenovirus infections, we choose a placebo as the standard treatment.

After randomization, the treatment will be administered and clinicians will provide patient's parents with a diary in which they will record the following informations every 6 hours for the first 24 hours then at 48 and 72 hours of observation from the administration of the drug or placebo:

- body temperature
- any medications
- pain
- nutrition

At the end of the 72 hours after randomisation, the parents will send the diary by post.

Setting

S.C. of Emergency Pediatrics of the A.O.U. Città della Salute e della Scienza di Torino, Regina Margherita Children's Hospital.

Eligibility criteria

Criteria for inclusion:

- Age between 6 months and 6 years (body weight between 5 and 27 kg).
- Body temperature (BD) measured with an axillary or ear thermometer of more than 37.5 vol. persisted for a period of at least 6 hours to a maximum of 5 days.
- Clinical presentation consistent with adenovirus infection of the pharyngeal tonsils, including at least one of the following symptoms: pharyngodynia/asthenia/hyporexia/nausea/vomiting/diarrhea/cough/rhinorrhea/abdominal pain/ earache. and at least one of the following signs: pharyngeal hyperemia with or without pharyngo-tonsillar exudate/inflammation of the upper or lower airways/lymphadenopathy/skin rash.
- Positive result on the antigenic test for adenovirus performed with with the "Biosensor" rapid swab.

- Negative result on the swab for Group A Streptococcus (GABHS), if deemed necessary according to McIsaac criteria (Appendix A1).
- Informed consent form for participation in the studysigned by the parent/s or other holder of parental responsibility.

Criteria for exclusion:

- Administration of betamethasone in appropriate dose according to weight in the last 48 hours.
- Chronic underlying disease associated with an increased risk of unusual or severe adenoviral infection.
- Inability to tolerate oral medication.
- Documented allergy or other known contraindication to the medicinal product Bentelan 0.5 mg.
  Patients on chronic therapy with anticholinesterase, salicylates, nonsteroidal anti-inflammatory drugs, thiazides, furosemide, amphotericin, xanthines (theophylline), antidiabetic drugs, insulin, cyclosporine, ritonavir, ketoconazole, acetylsalicylic acid, phenytoin, phenobarbitone, ephedrine, rifampin, blood thinners.) Subacute or chronic conditions requiring higher dosage of betamethasone orknown primary or secondary adrenal insufficiency.
- Transfer to another hospital for any reasons.
- Parents unable to understand the proposed study or who cannot reliably participate in the telephone follow-up due to significant language barriers.
- Participation in another study with the experimental drug within 30 days prior to and during this study.

Intervention

The intervention involves a single administration of a drug or placebo.

The experimental treatment consists of the active substance betamethasone, in particular the medicinal product Bentelan 0.5mg effervescent tablets is used. The drug is administered according to the weight classes shown in Table 1.

Weight in kg	Betamethasone dose in mg
5-<7	0.5
7-<12	1
12-<17	1.5
17-<22	2
22-<27	2.5

Table 1. Dosage of the medicine by weight classes.

The effervescent tablets of Bentelan 0.5mg are taken as required by SCP according to the above dosage regimen.

This dosing regimen allows the maintenance of doses between 0.1-0.2 mg/kg as indicated by SCP [9].

The placebo used in the study consist of 100 ml BBU ppi water. The water is administered in the same way as the experimental treatment. As it is odorless, tasteless and has the same appearance, it will not be recognizable by the parents. In terms of patients, the study population consist mainly of infants and preschool children, an age group in which the palatability of the drug is perceived as to match that of water.

In addition to IMP/placebo, an antipyretic therapy (paracetamol or ibuprofen) may be administered according to the dosage and timing of each active ingredient, depending on the patient's weight.

Primary outcome

The primary outcome is the proportion of patients with sustained fever reduction, i.e. in other words the proportion of patients who have a body temperature (BD) of < 37° C 18 and 24 hours after randomization.

Secondary outcome

Secondary outcomes include:

- Pharyngeal-tonsillar pain level (Depending on the age of the patients, the pharyngeal-tonsillar pain level was measured using different scales: the FLACC scale for patients younger than 36 months and the Faces Pain Rating Scale (Wong-Baker Scale) for patients of 36 months or older.)
- Hospitalisation (The proportion of patients admitted after an emergency access)
- Lenght of hospital stay (for hospitalised patients) defined as the number of days from the date of admission to the date of discharge.
- Cumulative incidence of fever resolution, is measured from randomization to fever resolution confirmed by measurement at the later timepoint; patients without fever resolution at the time of the last fever measurement are censored at this time-point.
- Fever duration is defined as the number of hours/days from the date of randomization to the day of the last measurement that resulted in a fever of more than 37,5°.

Timeline

Below the table with the protocol timeline (table n. 2)

Assessments	**Hours in the trial**								
Clinical visit	**Enrollment**	**Randomization**	**Post-allocation**						**Closure**
Phone call									
Clinical or phone assessment									
Hours in the trial		1	12	18	24	36	48	72	72
Participation in the trial									
Eligibility screening	X								
Parent/guardian information sheet	X								
Informed consent	X								
Drug delivery		X							
Drug administration									
Clinical Assessment									
Medical history		X							
Physical examination		X							
Temperature		X	X	X	X	X	X	X	
Vital parameters		X							
Symptoms and clinical signs		X							
Record of concomitant care or healthcare utilization		X	X	X	X	X	X	X	
Table to be completed (CT, general clinical conditions, nutrition)			X	X	X	X	X	X	
Laboratory Assessments									
Throat swab for adenovirus		X							
SBEGA throat swab		(X)							
Hematological tests		(X)							

Table 2, legend:(X) =indicates the tests that can be performed if the condition of the child requires it but are not mandatory.

Suitable children are identified in the emergency department as soon as an adenoviral infection has been diagnosed. The following data will be collected on admission:

-Medical history

-Physical examination

-BD

-Vital signs

-Clinical signs and symptoms

-Current therapies

No blood chemistry tests are required for the study. These can only be performed the doctor deems it necessary due to the patient's clinical condition. In this case the blood sample is taken according to the following table (Table No 3)

Weight (kg)	Total circulating blood volume (ml)	Maximum volume of sample allowed in 4 weeks (ml) - 3% of the total volume of blood	Maximum permitted volume of a single sample (ml) - 1% of the total volume of blood
0.5 - 1.5	50 - 150	1.5 - 4.5	0.5 - 1.5
2.5 - 5	250 - 500	7.5 - 15	2.5 - 5
5 - 12	480 - 960	14.4 - 28.8	4.8 - 9.6
12 - 20	960 - 1600	28.8 - 48	9.6 -16
20 - 30	1600 - 2400	48 -72	16 - 24

Table 3 from "Ethical considerations for clinical trials on medicinal products conducted with minors".

Patients who are discharged home are contacted by telephone after 24 and 72 hours after drug administration, to obtain an update on clinical progress. Patients who are hospitalised are clinically examined by the doctor after 24 and 72 hours and until discharge. If the hospitalised patients are discharged before 24 or 72 hours after drug administration, they will be contacted by telephone after 24 and72 hours after drug administration.

The end of the observation for each patient is 10 days after randomization. The parents of the patients will be contacted by phone for clinical updates (body temperature, nutrition) and the need for a visit in presence will be assessed.

Sample size

The study sample size was calculated to evaluate increase of proportion with a persistent fever resolution of 30%, approximately from 60% to 90%, with a power = 0.80 and a 2-tail alpha error of 0·05. A sample size of 80 patients was estimated (40 for each arm).

Randomization

Randomization will be stratified according to:

- the number of previous days with fever before entering the emergency department (≤48 hours, >48 hours),
- the administration of antibiotic therapy in progress or started in hospital (yes, no),
- the age (<3; ≥3 years) in view of the different scale of pain detection in these two age groups.

The allocation rate will be 1:1The Clinical Epidemiology unit of AOU Città della Salute e della Scienza in Turin will carry out all procedures for the generation and management of randomisation in a way that is not foreseeable by the staff involved in the study.

Sequence generation will be based on computerised procedures, with variable length blocks in random order.

The randomization procedure will be made available continuously (24/7) by the SSD Clinical Epidemiology unit of the AOU Città della Salute e della Scienza di Torino via a web platform with an area reserved for the study, and allocation will take place after the recording of the necessary data (patient ID, stratification variables).

Masking (Blindness)

As the aqueous solution of IMP and the placebo (water ppi) are administered identically and both are colourless, odorless and tasteless, parents and patients are unable to distinguish between the two solutions.

The study design stipulates that patients, parents (or other persons with parental responsibility), researcher do not know which treatment arm to which the patient is allocated to (double-blind study). Only the nursing staff who are responsible for administering the treatment know the treatment arm.

If necessary, after having authenticated themselves with the web platform that manages the randomisation, the doctors can request the opening of the blind, by indicating the patient code and the reason for the opening. The platform keeps track of all requests to open the blind.

The unmasking of the individual patient does not lead to the unmasking of the other participants.

Data collection

BT will be measured by healthcare professionals in the hospital with an axillary thermometer ("Digi-Temp digital thermometer", manufacturer Med's) or with a headset ("Genius 3 tympanic Thermometer and base" manufacturer Covidien). At home the same analogue thermometer "Pic Solution Digital Thermometer Vedo Family" (manufacturer "Pic Solution", model PIC0100044/4) will be used by all families and will be provided to parents at the time of enrollment.

Parents will also receive a diary (Appendix No. 3) to record the following parameters every 6 hours for the first 24 hours and then at 48 and 72 hours after the administration of the drug or placebo:

-BT measurements prior to any concomitant treatment,

-the level of pharyngeal tonsil pain measured by the FLACC or Wong-Baker scale,

-nutrition (absent, reduced, normal),

-All other medications and dosages administered during the observation hours of the study,

-any adverse reactions or events that may occue during observation.

The degree of pharyngeal tonsillar pain is assessed by the parents at home and by the clinical staff at the hospital using pain scales depending on the age of the child.

If the age of the child is between 2 months and 35 months, the FLACC scale, a hetero evaluation scale for measuring pain in children[7](Appendix A2), is used. It is based on five parameters (facial expression, legs, activity, crying, comfort), each scored from 0 to 2, up to a maximum total score of 10 (which corresponds to the worst possible pain).

If the child's age is between 36 months and 6 years, the Faces Pain Rating Scale (Wong-Baker Scale) is used, a self-assessment scale in which the child recognises the intensity of his pain by choosing from a series of six smiles the one that best expresses his pain, from the smiley face, corresponding to the absence of pain (0), to the crying face, corresponding to the worst possible pain (10). The score corresponding to the selected face indicates the intensity of the pain experienced[8] (Appendix A3).

Families will be contacted by telephone 24 and 72 hours after randomization to identify any reactions or adverse events and to provide the necessary support.

If the patient needs to be hospitalised, clinical observation and diary compilation may be requested to the parent or performed directly by the doctor.

10 days after randomization, an "end of study" telephone consultation is scheduled to identify any reactions or adverse events and to provide the necessary support. During the "end-of-study" telephone consultation, the need for a follow-up visit with the patient's family will be considered, if deemed appropriate.

Methods of data collection

All sensitive data is stored in a password-protected computer database, in accordance with the procedures already in place at the SC Paediatrics Emergency City of Health and Science Turin, in full respect of the law and the patient's privacy. The database, which can only be accessed by the staff responsible for the study, is stored on a dedicated computer that is not connected to the network and is password-protected. The data from this project is collected in encrypted files (authorisation levels, passwords, back-up).

On admission to the Emergency department, the families of children who fulfil the above-mentioned admission criteria, will be informed about the study and the possibility of participating by a patient information leaflet and providing oral information.

If the parent/parents agree to participate in the study, they will be asked to sign an informed consent form (Annex No.2).

If the patient is discharged home, a paper diary (Annex No. 3) is given to the parent/parents, to fill in at home.
The diary must be returned to the investigator by ordinary post to the sender SC of Emergency Pediatrics, Children's Hospital Regina Margherita - AOU Città della Salute e della Scienza, Piazza Polonia n. 94, 10126 Turin.
Parents will receive an envelope with a postage address and stamp, to facilitate dispatch.

Statistical Methods
All randomized subjects will be included in the primary efficacy analysis according to the randomization arm, regardless of the use of the therapy in study (intention-to-treat analysis).
The proportion of patients with persistent fever resolution at 18 hours (primary outcome) from randomization in the two randomization arms will be compared using the Mantel-Haenszel stratified test, taking into account the stratification variables defined for randomization. The same approach will be used to compare the proportion of children needing hospitalisation. The secondary outcomes, defined on an ordinal scale (FLACC/Wong-Baker score and length of hospitalization) will be compared using a ordinal logistic regression model by adjusting for stratification variables. The cumulative incidence of fever resolution will be compared using the stratified log-rank test. Sensitivity analysis will be performed with multivariate regression models that take into account the

type of outcome variables (dichotomous, ordinal, time to event) and adjuste the comparison of the randomization arms for the stratification variables and the main prognostic factors.
The subgroup analysis for the primary outcome will be performed in relation to the stratification variables, with the logistic regression model including an interaction term between the variable identifying the randomization arm and that of the subgroup of interest.

Reference Safety Information (RSI)

To describe the nature and severity of adverse events (recorded by parents at home or by hospital staff for inpatients), the classification of toxicity provided in version 5.0 of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) will be used (For definitions of adverse event, serious adverse event, serious adverse reaction and serious adverse reaction, assessment of severity and randomness see Appendix 4)

A special section for the reporting of suspected adverse events was prepared in the data collection form (CRF).

A specific Serious Adverse Events (SAE) reporting form has been prepared and will be sent to the Office of Corporate Pharmacovigilance: FVG_studiclinici@cittàdellasalute.to.it.

The nature and frequency of adverse events will be monitored on the basis of the summary of product characteristics of the medicinal product Bentelan 0,5 mg.[9]

SAE/SUSAR reporting

The investigator must notify the sponsor within 24 hours of becoming aware of a serious adverse event. In the event of a death, the Ethics Committee will also be informed. The SUSAR must be reported to Eudravigilance within the following deadlines:

- Fatal or life-threatening SUSAR within 7 days
- All other SUSARS within 15 days.

Non-serious adverse events (AEs) and non-serious adverse reactions (ARs): All non-serious adverse events and non-serious adverse reactions occurring during the treatment period should be reported in the CRF.

Serious Adverse Events (SAEs) or Suspected Unexpected Adverse Reactions (SUSARs): All SAE/SUSAR, whether or not related to therapy, that occur during treatment or within 30 days of the last administration of the drug provided for in the protocol must be reported on a special form and emailed to FVGexperimentation@cittadellasalute.to.it within 24 hours of becoming aware of the event. The information on the SAE form can be written in Italian. The initial SAE Form must be completed in full; the information that was not available at the time the original form was drawn up must be described in the Follow-Up Forms and sent to the sponsor.

The sponsor is responsible for the appropriate and timely reporting of SUSAR adverse reactions in accordance with local regulatory procedures. The sponsor must report all SUSAR reported during the clinical trial to the relevant regulatory authorities, Ethics Committees and Investigators at the other centres involved.

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established, consisting of experts independent of the sponsor, who will assess the safety data of the study at regular intervals during the study to recommend whether the study should be continue, modified or closed.

The DSMB will have access to detailed reports detailing the incidence and type of reported serious adverse events. The timing of the assessment will depend on the enrolment rate of the study, the type of adverse events occurring and the DSMB's monitoring recommendations.

After each assessment, the DSMB will prepare a report and may recommend changes in the conduct of the study.

Assessment of foreseeable benefits and risks

The use of betamethasone during an adenoviral infection can lead to rapid improvement in the patient's clinical condition and a reduction in hospitalisation. The findings from this study could be beneficial for this patient group in the future.

There is a possibility that patients participating in the study may experience side effects from the medication Bentelan 0.5 mg®, which is the subject of the study.

It is emphasised that the drug is already used in normal clinical practise and that a single dose will be administered.

Measures to minimise the risk

Risk minimisation measures aim to optimise the safe and effective use of a medicinal product. Routine risk minimisation measures include the use of tools such as the Summary of Product Characteristics (SPC), the package leaflet, labelling and the medicinal product supply regime. No additional measures are planned in this study, as the drug under investigation will be administered once at a therapeutic dosage according to CPR and no further administration is planned.

Good Clinical Practice and Privacy Policy

This study will be conducted in accordance with the principles of Good Clinical Practice [ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996 Directive 91/507/EEC; D.M. 15.7.1997], the Helsinki Declaration and the national rules on the conduct of clinical trials. By signing the protocol, the investigator agrees to comply with the procedures and instructions contained therein and to conduct the study in accordance with GCP, the Helsinki Declaration and the national regulations for clinical trials.
Participants will be informed of their right to privacy and the handling of personal data collected, in accordance with to art. 25 and 32 of EU Regulation 2016/679 (GDPR) to ensure the confidentiality and security of information.

Ethics committee and informed consent

The treating specialist doctor will give the parents/ legal guardians an informed consent form, as part of the care provided in the emergency department.
In this context, the patient will be offered the opportunity to participate in the research project, after the objective analysis of the specialist. To this end, the research areas and possible outcomes of the study will be explained in a simple manner.
Informed consent will be obtained using the information sheet and the attached template.
All information about the study and the proposal to participate in it will be provided to the parents or legal guardians in a clear, understandable, objective, truthful and comprehensive form. The same information may be provided to the patient in simple, age-appropriate language, if applicable.

Any patient can may discontinue participation in the study at any time without consequences for the safety and efficacy of the treatment. In this case, parents will be asked to indicate whether the data collected up to that point can still be used for the purposes of the study or whether it should be excluded. This option will be clearly explained at the time informed consent is obtained.

Closure or interruption of the study

The study will be closed 10 days after the last patient who participated in the study. The study may be terminated early according to the judgement of the DSMB.

Documentation archive

The investigator is responsible for the storage and preservation of the essential documents of the study before, during and after the completion or interruption of the study, in accordance with the applicable legislation and GCP guidelines and for the intended period of time.
The investigator retains the original patient data (e.g. demographic and medical information, laboratory data, etc.) and a copy of the signed written informed consent formsin a secure file.

Publication of results

The results of the study will be made available within 12 months of the end of the trial.

Confidentiality and Confidentiality

The study documents will stored in a secure location to ensure confidentiality and secrecy and may not be disclosed to third party without written authorisation from the sponsor except to the extent necessary to obtain patient's consent to participate in the study.

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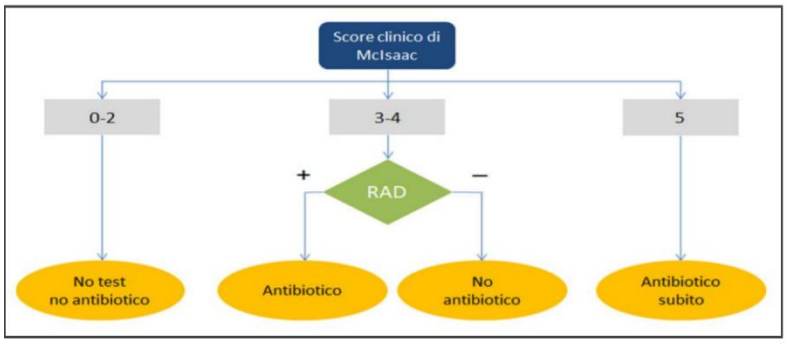
https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004375_019655_RCP.pdf&sys=m0b1l3

Appendix A1

Score by McIsaac

Source: Warren J McIsaac 1, James D Kellner, Peggy Aufricht, Anita Vanjaka, Donald E Low. Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA. 2004 Apr 7;291(13):1587-95.

Score di McIsaac	Punti
Febbre (T > 38°C)	1
Assenza di tosse	1
Linfopatia laterocervicale anteriore dolente	1
Tumefazione o essudato tonsillare	1
Età 3–14 anni	1



Appendix A2

Scala FLACC

Source: *PAIN IN THE CHILD Practical Tools Evaluation and Therapy Ministry of Health Ministry of Health.*

Category	0	1	2
Face (Face)	Neutral expression or smile	Occasional grimaces or wrinkled eyebrows, expression disinterested, detached	Frequent to constant aggrotting of eyebrows, closed mouth, chin tremor
Legs (Legs)	Normal or relaxed position	He gets agitated, restless, tense	Kicks straighten your legs
Activity (Activity)	Quiet position, normal, moves in natural way	It twitches, it swings back and forth, tense	Arched, rigid, it moves to snaps
Weeping (Cry)	Absence of weeping (during a vigil or sleep)	He groans or whimpers, whining	She cries constantly, screams or hiccups, whining frequent
Consulability (Consolability)	Satisfied, relaxed	Reassured by contact occasional, embrace, tone of voice; distractible	Difficult to console or comfort

Appendix A3

Faces Pain Rating Scale (Wong Baker scale)

Source: Wong DL,Baker CM, Pediatric Nursing 1988; 14:9-17

Appendix 4 Safety Information

Definitions of adverse event, serious adverse advent, adverse reaction. Serious Adverse Reaction

In the context of this study, we use the following definitions in accordance with "Detailed guidance on the collection, verification and reporting of adverse events or adverse reactions arising from the clinical trial of medicinal products for human use" (CT-3):

- **Adverse event (AE):** Any unwanted medical event that occurs during the clinical trial with the drug under study, regardless of whether there is a causal link with treatment. Adverse events may include both predictable and unpredictable reactions.
- **Serious adverse event (SAE):** An adverse event that meets at least one of the following criteria: causes death, endangers the life of the participant, requires hospitalization or prolongation of the pre-existing hospitalization, causes a significant or permanent disability, or other medical conditions that require specific medical action to prevent permanent harm.
- **Adverse reaction (AR):** A reasonably possible causal relationship between treatment with the study drug and an adverse event.
- **Serious adverse reaction (SAR):** An adverse reaction that meets the criteria of a serious adverse event.
- **Unexpected and serious adverse event (SUSAR):** A serious adverse event that occurs unexpectedly and is subject to immediate reporting to the competent regulatory authority.

Gravity

The severity of adverse events not listed in the NCI CTCAE term toxicity scale will be assessed on the basis of the following levels:

- Mild (grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention needed.
- Moderate (grade 2): minimal, local or non-invasive intervention indicated; limitation of age-appropriate instrumental activities of daily life (ADL).
- Severe (grade 3): clinically significant, but not immediately life-threatening; indication of hospitalization or extension of hospitalization; disabling; limitation of personal care ADL.
- Life-threatening (grade 4): substantial risk of death at the time of the event. Urgent intervention indicated.
- Death (grade 5): AE-related death

Causality

The Investigator will make an assessment of the causality between the adverse event (AE) and the treatment. Regardless of the dose administered, the following considerations will apply:

- **Unrelated**: When AE is not considered to be treatment related.
- **Possible correlation:** When a causal link between the EA and the treatment is made probable based on the temporal relationship and the nature of the event.

Predictability

If the EA is judged to be treatment-related, the Investigator shall assess its predictability based on known safety information. The EA will be classified as:

- **Expected**: The reaction is consistent with available information on treatment toxicity.
- **Unexpected**: The reaction is inconsistent with the available information on treatment toxicity.