COVER PAGE

Official title: "FIVE-YEAR SINGLE-BLIND, PHASE III EFFECTIVENESS RANDOMISED ACTIVELY CONTROLLED CLINICAL TRIAL IN NEW ONSET JUVENILE DERMATOMYOSITIS: PREDNISONE VERSUS PREDNISONE PLUS CYCLOSPORINE A VERSUS PREDNISONE PLUS METHOTREXATE"

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ABSTRACT

[Full title] Five-year single-blind, phase III effectiveness randomised actively controlled clinical trial in new onset juvenile dermatomyositis (JDM): prednisone (PDN) versus PDN plus cyclosporine a (CSA) versus PDN plus methotrexate

[Acronym] PRINTO JDM trial

Abstract

Scientific objectives: The proposed project is aimed to improve treatment approaches for rare, severe and disabling paediatric rheumatic diseases (PRD). This goal will be achieved by the Paediatric Rheumatology International Trials Organisation (PRINTO) an international network whose main function is to provide a scientific base for current PRD treatments for which no evidence based data exist in the literature, and for drugs for which there is no support from industries.

This is a 5-year project, involving 185 partners from 46 countries (110 in 21 EU States and 75 in 25 extra-EU States), with a randomised clinical trials (RCT) in juvenile dermatomyositis (JDM): 5-year phase III single-blind, RCT in children with newly diagnosed JDM: prednisone (PDN) versus PDN plus methotrexate (MTX) versus PDN plus Cyclosporine A. The trial is aimed to find out the treatment regimen associated with the lowest occurrence of flare and the lowest drug related toxicity. **The retention on treatment will be used as main measure of effectiveness.**

Methodology: The present protocol is the natural follow up of previous work conducted by PRINTO. In particular the RCT foreseen in this protocol is modelled after the successful completion of an early phase trial with MTX in juvenile idiopathic arthritis, and will use validated JDM outcome measures for the evaluation of response to therapy.

It is the basic premise of this protocol that, without i) the involvement of the international paediatric rheumatology community, ii) the innovative type of mechanism described herein, these studies would never be conducted.

INTRODUCTION

Paediatric rheumatic diseases (PRD) are rare conditions, associated with substantial morbidity, and monetary costs. Drugs for the treatment of PRD are now being used in new dosages and administration routes, new combinations and for disease complications. There is, however, little incentive for pharmaceutical companies to fund large-scale trials of these new approaches. Consequently, data regarding the safety and efficacy of treatment regimens tends to be from anecdotal, small, uncontrolled, non-randomised case series.
In order to attempt to resolve the above problems, the Paediatric Rheumatology International Trials Organisation (PRINTO) (1) was founded in 1996 initially by centres from 14 European countries; the network now includes more than 200 paediatric rheumatology centres from 45 countries worldwide. Notably, a total of 185 from 46 countries are partners in this protocol. PRINTO's aims are to facilitate and co-ordinate the development, conduct, analysis, and reporting of clinical trials and to evaluate short and long term outcome of children with PRD. The general philosophy behind the PRINTO work is very well summarised by the list of grants obtained so far from the European Union (EU).
With a first project, PRINTO was able to successfully address (2) the shortcomings of performing phase III clinical trials for juvenile idiopathic arthritis (JIA), and to provide cross-culturally adapted and validated tools for health related quality of life assessment in children with chronic conditions (3).
With a second project PRINTO successfully addressed the lack of standardized and validated measures for the evaluation of response to therapy in juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM) (4).
Moreover with a third project, PRINTO was able to enhance families participation in clinical trials through the establishment of a web site translated into 50 languages (www.pediatric-rheumatology.printo.it) (5) where standardises and up to date information about the PRD can be found.
Finally PRINTO with a still ongoing project PRINTO is in the position to offer research training to physicians from developing Latin American countries in order to enhance their participation in international collaborative studies.

Objectives. The goals of the current protocol is therefore the natural follow-up of the objectives achieved with the previous grants and, in particular, of projects designed to discern new models for the successful conduct of clinical trials in children with rare diseases, and to develop standardized and validated measures for the evaluation of response to therapy in JDM.
The proposed trial in JDM (prednisone [PDN] versus PDN plus methotrexate [MTX] versus PDN plus cyclosporine [CsA]), should serve as a model for the successful running of early phase clinical trials for severe and disabling rare diseases of childhood.
The ultimate aim of these trials is to provide evidence-based information about the clinical utility of drugs in the management of rare paediatric conditions.

PROTOCOL

The proposed trial in JDM is to serve as a methodological prototype for future early phase clinical trials in the field of rare diseases of childhood, and they will be used to test the mechanism whereby these studies will be done. Future studies could be considered appropriate for consideration by paediatric networks only if:

1) the new therapeutic is deemed to have legitimate promise of being effective and safe (risk/benefit ration);
2) the trial will not be fundable by conventional means (i.e. pharmaceutical industry);
3) the usual method of cost reimbursement for clinical care will bear the patient expenses.

It is anticipated that most trials will be actively randomised controlled clinical trials.
Personnel at the coordinating centre will assist principal investigators in protocol development, and provide the expertise and facilities to initiate the trial, recruit subjects, gather and analyze data and report results.
The proposed trials were selected by the PRINTO network Advisory Council, after a survey of practicing paediatric rheumatologists from all over the world.

Results of the feasibility survey. A survey on the willingness to participate in the JDM trial was sent to 252 centres in 46 countries. The overall response rate to the survey of 211/252 (84%). A total of 170 centres from 46 countries worldwide (in 21 European States and 25 States outside the European Union) agreed to participate and are now part of this protocol. Below are the results of the feasibility survey

	JDM
Total responding to the survey	211/252 (84%)
Willing to participate	170/211 (81%)
Not willing to participate	41/211 (19%)
No. of potential eligible children in 1 year (min-max)	193-482
Median no of eligible children per centre in 1 year (min-max)	1-3

FIVE-YEAR SINGLE-BLIND, PHASE III EFFECTIVENESS RANDOMISED ACTIVELY CONTROLLED CLINICAL TRIAL IN NEW ONSET JUVENILE DERMATOMYOSITIS (JDM): PREDNISONE (PDN) VERSUS PDN PLUS CYCLOSPORINE A (CSA) VERSUS PDN PLUS METHOTREXATE

Introduction: Juvenile dermatomyositis (JDM) is a multisystem disease characterised by acute and chronic non-suppurative inflammation of striated muscles and skin. The disease is marked early in its course by the presence of a vasculopathy of varying severity that can be widespread and sometime also fatal, and late by the development of dystrophic calcinosis (that is more frequent in children than in adults) (6-9). Although JDM is a rare disease, it is the most common of the pediatric inflammatory myopathies, with an incidence of 3.2 cases/1 million children/year (6;10;11) fulfilling the diagnostic criteria of Bohan and Peter (12;13). Disease duration in JDM ranges from <1.0 year to persistent disease beginning during childhood but lasting well into adulthood (7-9;14-16). Death has been reported to occur in up to 39% of children with JDM (16) with most studies reporting mortality rates between 3-18% (6-9;14). However, even for those surviving the illness, there are often chronic complications and long-lasting disability. In one long-term study that followed childhood onset JDM patients into adulthood, 33% still demonstrated weakness, 39% still had dermatologic manifestations, 22% had persistent contractures, and 39% had subcutaneous calcinosis (8). In another study of childhood onset JDM patients evaluated at a mean age of 18.8 years, 33% reported limitations in ability to do daily activities, 78% still had dermatologic manifestations, 58% had additional nondermatologic abnormalities on physical exam, and 50% had evidence of muscle scarring by ultrasound evaluation (7).

Current available treatments in children: the treatment of JDM, is unsatisfactory, and corticosteroids are the only agents currently approved by the US Food and Drug Administration for myositis. Prednisone therapy is frequently required for long periods with a mean duration ranging from 25 to 54 months (7). In some series, over 40% of the JDM subjects remain on prednisone for more than 7 years (7;17). Many of JDM patients fail to respond adequately to corticosteroids and require additional immunosuppressive medications, none of which have been tested in controlled trials in this conditions (6;9;10;16;17). Indeed no randomised clinical trial with immunosuppressive agents are available for children with JDM, and most of the studies involve single referral centres reporting retrospectively on small numbers of patients followed for relatively brief periods of time (18-24). Few examples are reported in the following paragraphs.

The duration of prednisone treatment was studied retrospectively in children with JDM treated by two different methods, PDN alone versus MTX and PDN (17). The authors concluded that in this short-term comparison, early use of MTX allowed for acceptable clinical outcomes with much shorter duration of prednisone treatment. This study suggests a significant prednisone sparing effect with the early introduction of MTX in the treatment of JDM. Similar conclusions were reported by others (18;21).

In other 2 studies cyclosporine A (CsA) has been used to treat patients with refractory JDM (23;24); the Authors concluded that CsA represents a promising agent for the treatment JDM. Although suggestive, these trials have significant design limitations, small sample size, they lack standardised measures to evaluate the outcome, and they do not have a standardised protocols for prednisone tapering.

As a conclusion it can be stated that current treatment for JDM has failed to eliminate significant morbidity and mortality and that although several publications describe experience with second line agents no prospective randomized trial has ever been performed in children with JDM.

Trial Objective. To assess the **effectiveness** (efficacy, safety, tolerability and compliance to treatment) of the 3 treatment approaches for the treatment of children with JDM.
THE OVERALL HYPOTHESIS TO BE TESTED IN THIS TRIAL is that the early introduction of combination therapy of corticosteroids and either MTX or CsA will prove more effective and safe than corticosteroids alone in the treatment of JDM.

Trial Design and Duration. Two-year single-blind (assessor blinded to treatment arm of subject), randomised, actively controlled, multi-centre, international prospective, superiority trial of different combination of drugs. Patients will be then followed for up to 5 years for the evaluation of long term morbidity and mortality.

Dose Regimen (see figure 1):
3 daily pulses of intravenous (iv) methylprednisolone (30 mg/kg/pulse max 1 g/pulse) followed by randomisation into one of these 3 groups.

Induction of remission

Group 1 prednisone or equivalent (PDN): PDN 2 mg/kg/day (see below for rules regarding PDN administration);
Group 2 PDN+cyclosporine A (CsA): PDN 2 mg/kg/day + CsA 5 mg/kg/day in 2 oral doses.;
Group 3 PDN + methotrexate (MTX): PDN 2 mg/kg/day + MTX 15-20 mg/m^2 once per week. Patients treated with MTX will receive concomitant folic or folinic acid according to the attending physician decision.

Suggested PDN administration for all 3 groups: From a survey conducted in USA high dose corticosteroids are used as initial treatment of choice by 76% of the paediatric rheumatologists (personal communication), justifying therefore the inclusion of this arm in the trial. After randomisation all patients in the 3 groups will receive 2 mg/kg/day of PDN or its equivalents. In the first month, PDN will be administered in 3 divided daily doses (oral preferentially). Starting at month 2, PDN will be administered orally in a single daily dose in the morning, and tapered, if allowed by clinical status, by 0,25 mg/kg every week to reach a daily dose of 1 mg/kg/day at the end of month 2. Then until the end of month 6, PDN should be tapered, if allowed by clinical status, to reach a daily dose of 0.2 mg/kg at the end of month 6. Starting at month 7 all patients will receive a daily dose of 0.2 mg/kg/day, that will be maintained until the end of month 12. Starting at month 13 the PDN dose will be reduced to 0.1 mg/kg/day for further 6 months and then to every-other-day regimen at a dose of 0.1 mg/kg/day until month 24. If the patient will reach clinical remission before month 24, PDN will be withdrawn earlier than the suggested schedule of PDN administration. For prevention of osteoporis patients can be treated with calcium and vitamin D supplementation according to the attending physician decision.

Suggested CsA administration: CsA will be administered orally at 4-5 mg/kg/day in 2 divided dose. If serum creatinine will rise > 30% of baseline value CsA dose will be reduced by 1-2 mg/kg/day (depending on severity) for 1 month. If after 1 month serum creatinine will return < 30% of baseline value CsA can be continued at the same lower dose. If after 1 month serum creatinine will remain > 30% of baseline value stop CsA for 1 month and then check again serum creatinine: a) if serum creatine after 1 month stop of CsA return within 10% of baseline value CsA can be restarted at 3 mg and increased to the maximum tolerated dose (depending on serum creatinine level); b) if serum creatine after 1 month stop of CsA still remain > 10% of baseline value CsA stop definitively.

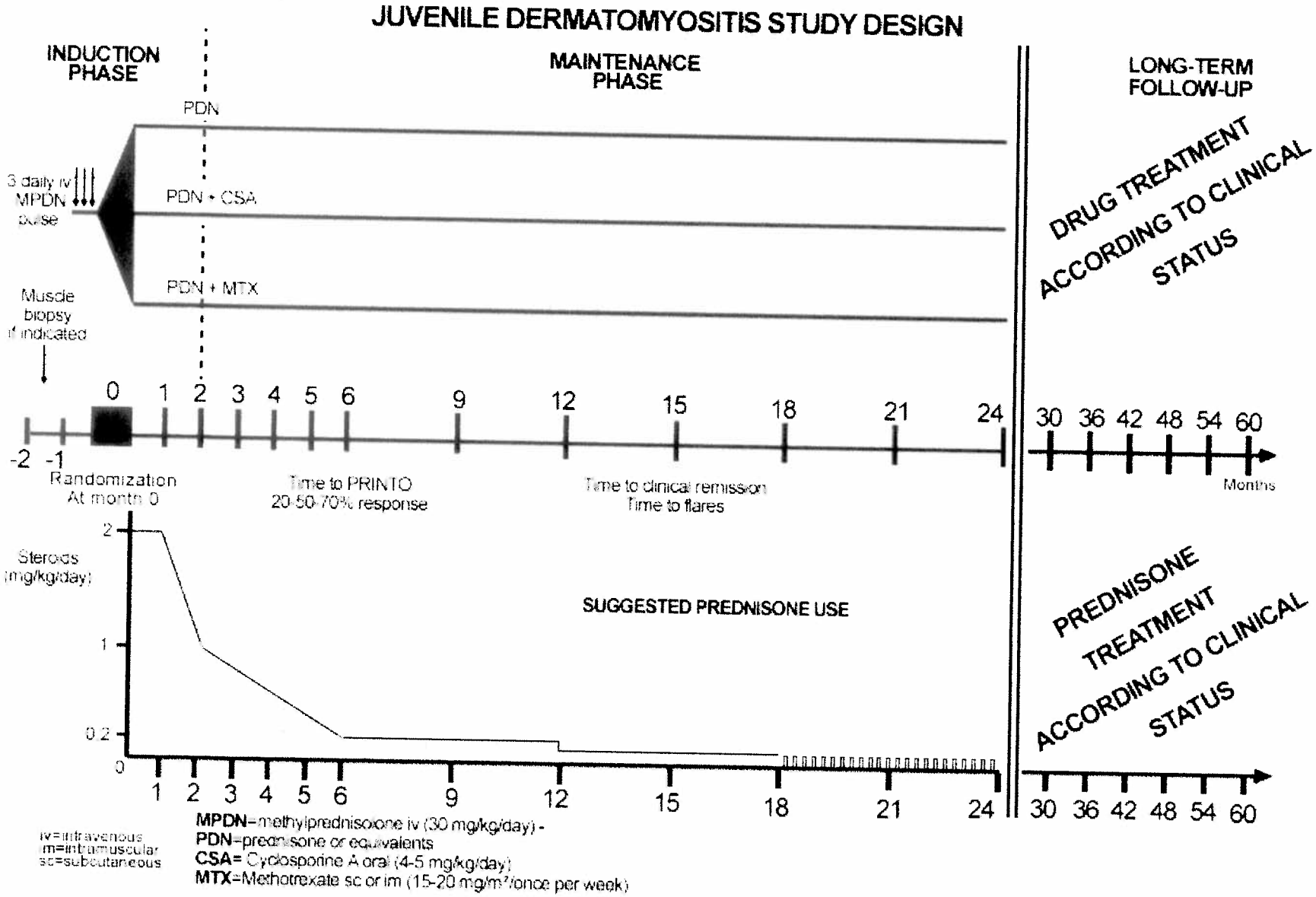
Suggested MTX administration: MTX will be administered parenterally (subcutaneously, intramuscularly) at 15-20 mg/m^2 once per week. In case of MTX related toxicity (eg transaminase increase) stop MTX for 2 weeks and if adverse event disappear start again at 10 mg/m^2 once per week and increase of 2.5 mg/m^2 once per week every week until the maximum tolerated dose (max 20 mg/m^2 once per week). If adverse event persist stop methotrexate. Patients treated with MTX will receive concomitant folic (1 mg/day except the day of MTX administration) or folinic acid (25-50% of the MTX dose in mg; to be administered the day after MTX administration) according to the attending physician decision.

Long term follow up after month 24 until month 60. All patients will be followed for a total of 5 years for the assessment of long term morbidity and mortality rate. After month 24 treatment will be left open to the physician decision based on the clinical status of the patient.

Important: Medications will be supplied by the pharmacy of the participating centre and covered with the standard way of reimbursement in each participating country.

Subject Population. Newly diagnosed and untreated children with probable or definite diagnosis of JDM according to Bohan and Peter Criteria (12;13).

Figure 1: JDM study design



Efficacy Parameters:

Primary Outcome Measures after 6 months of treatment. According to the PRINTO definition of improvement for JDM, patients will be considered responders to therapy if they will demonstrate at least 20% improvement in at least 3 core set variables with no more than 1 of the remaining variables, (muscle strength excluded), worsened by > 30% (4).

The PRINTO JDM core set variables (4) are:

1) muscle strength by the mean of the Childhood Myositis Assessment Scale (CMAS);
2) physician's global assessment of disease activity on a 10 cm VAS ;
3) global disease activity assessment by the mean of the Disease Activity Index (DAS);
4) parent's/patient's global assessment of overall well-being on a 10 cm VAS;
5) functional ability assessment by the mean of the Childhood Health Assessment Questionnaire (CHAQ)
6) health-related quality of life assessment.

Primary Outcome Measures after 24 months of treatment: a) time to clinical remission on medication defined as normal muscle strength and physician global assessment of disease activity equal to 0; b) time to flare of the disease defined as at least 20%, worsening from the previous evaluation value in 2 of any 6 JDM core set measures with no more than 1 of the remaining improved by more than 30% (muscle strength excluded).

Effectiveness: the rate of retention on treatment will be used as main measure of effectiveness.

Secondary Outcome Measures. Change over time in the individual components of the JDM core set of variables; time to muscle enzymes normalisation; frequency of drop-out of suggested steroids use; frequency of drop-out for inefficacy of treatment.

Safety Parameters.

1) Incidence of adverse events (AE):
   a) Number of patients discontinuing trial due to on-therapy conditions and AE possibly, probably, or definitely related to the experimental therapy, and listing of AE that cause discontinuation.
   b) Number of patients for whom the dosage was lowered, or withheld temporarily, due to AE, and listing of the specific AE that caused such action.
   c) Complete list of AE by system.
2) Incidence of clinically significant changes in laboratory parameters.
3) Drop out rate due to toxicity.

Inclusion Criteria. Each patient must meet all the following criteria in order to participate in this trial:

1) Newly diagnosed and untreated children (only treatment with 1 NSAID is allowed and/or prednisone >1 mg/kg/day for no more than 1 month from diagnosis) with probable or definite diagnosis of JDM according to the Bohan and Peter criteria (12;13). If a muscle biopsy will be performed (optional) it will be read by the pathologists of the participating centres (light and immunofluorescence). Slides of paraffin-embedded sections from all patients will be re-viewed by a blinded myopathologist at PRINTO.
2) Age at enrolment ≤ 18 years.
3) Female of child-bearing potential must have a negative pregnancy test at the beginning of the trial, and then every 3 months. If sexually active, they must agree to use adequate contraception, throughout study participation, and must have no intention of conceiving during the course of the study. Post-pubertal males must have no plans to father a child during the study and agree to use adequate birth control methods if sexually active.
4) Ability to comply with the entire study procedures, ability to communicate meaningfully with the investigational staff, competence to give written informed consent; to be applied to the parents and/or patients, as appropriate
5) Duly executed, written, informed consent obtained from the parents/patient.

Exclusion Criteria. Any of the following will exclude a patient from this trial:

1) Neutrophil count <1,500/mm^3 and/or platelet count <50,000/mm^3
2) Demonstration of cutaneous or gastrointestinal ulceration of JDM related pulmonary disease or cardiomyopathy at the time of diagnosis.
3) History of poor compliance.
4) Evidence of current use of alcohol or illicit drugs abuse.
5) Live vaccines not allowed during the entire duration of the trial.

Dropout Criteria. Patients will be considered "treatment failures", and dropped from the trial but included in efficacy analysis, if any of the following will occur during the active period of the trial.

1) Non compliance with study medication administration
2) Enrolment in other therapeutic trials.

Feasibility study for sample size calculation: from the analysis of the 295 patients with JDM enrolled in a previous PRINTO study (EU contract QLG1-CT-2000-00514) (4) it can be inferred that the network can enrol in a 2 years frame up to 190 children with less than 12 months disease duration (of whom 140 with disease duration less than 6 months).

Sample size calculation for superiority trial. We used the PRINTO JDM definition of improvement (see previous section "definition for primary outcome") (4) for sample size calculation for superiority trials.

We carried out sample size calculations based on the information obtained from a study on JDM patients conducted by PRINTO with a previous grant (contract EU contract QLG1-CT-2000-00514). In the study a total of 284 JDM patients with a mean age at onset of 7.6 years (Standard Deviation [SD] 3.9) the observed improvement rate was 83% after 6 months of therapy with PDN combined with MTX or CSA. We estimated that the group treated only with PDN will have a response rate equal to 53%.

Using the sample size calculation for superiority trials and considering a drop out rate of 15%, a sample size of **40 patients in each group for a total of 120 patients**, will be required. The trial will have 0.8 power for comparisons of the combined treatment arms (PDN+MTX or PDN+CSA) to the reference treatment arm (PDN alone).

If enrolment will proceed faster than expected we will collect 54 patients per arm for a total of 162 patients, 0.9 power, 0.05 type I error.

Below is a table with different sample size calculations, using different levels of power.

Variable	PDN treatment	delta	alfa	Power	N per arm	Drop-out N/(1-0.15)
PRINTO JDM def.	53	30%	0.05	0.8	34	**40**
PRINTO JDM def.	53	30%	0.05	0.9	46	54

Procedures in the Case of Adverse Events. In the event of clinical or laboratory AE, the attending physician should make the clinical decision as to which medication is most likely the cause of the AE. The suspected medication (experimental or allowed) should be stopped or dosage reduced for 1 or 2 weeks. If the AE disappears or significantly ameliorates then the medication will be reinstated. If the AE does not disappear the physician will either drop the patient from the trial, or repeat the procedure with one of the remaining drugs. The drug that was initially discontinued (experimental or allowed) may be reinstated (as deemed appropriate by the attending physician), once it has been shown not to be the cause of the AE.

Withdrawal From the Trial. The attending physician will determine, clinically, if a patient should be removed from the trial, stating the reason for the early termination on the appropriate

form. The attending physician will be also responsible for reporting all clinically significant drug related AE. These will be graded on a three-point scale (mild, moderate, severe), and the relationship with the study medication will be assessed as definite, probable, possible, unlikely or no association as defined in the AE form. Any unexpected, life threatening or fatal AE will be reported by telephone within 12 hours after the AE, to the coordinating centre, followed by detailed medical description of the AE, along with copies of all pertinent medical records.

Clinical and laboratory evaluation. Monthly up to 6 months, then every 3 months up to 24 months, then every 6 months up to month 60.

Monitoring, Quality Assurance, Condition for Terminating Early the Trial. All forms will be reviewed by the coordinating centre for completeness and report of AE. Data will be double entered by 2 in a computer database. Random review of 10% of computer data entry will be double-checked after enrolment of 50% of the patients. Six months after enrolment of 50% of the patients, an independent Monitoring Board, will assess the necessity to continue the trial; if the difference between the 3 treatments is found to be so extremely significant ($p \leq 0.001$) that is virtually impossible to arise by chance alone than the trial will be terminated early. Compliance in the active period will be assessed by a weekly diary reporting the administered dose. Physicians will also solicit information on the concurrent medications.

Informed-Consent Documentation. Ethics Committee approved informed-consent will be obtained from parents or children of an appropriate age (translated in national languages).

Data Collection. One copy of the case report form will be collected via fax by the international coordinating centre of the European network; the original copy will be included in the medical records of the patients. In order to detect selection bias a rejection log will be maintained by each participating centre containing demographic data, disease characteristics, and a brief explanation as to why the examining physician decided to withhold the patient from the trial. English will be the official language used for all forms completed by the physicians while other forms filled by parents/patients will be translated into the national language of the patient.

Statistical Analysis. The values at the final visit for the core set variables will be compared to the baseline values. Furthermore, patients will be dichotomously classified as "responders" or "non-responders" according to the validated JDM definition of improvement. Descriptive statistics will be used for reporting adverse events. For proportional data the chi-square test, or where appropriate the Fisher's exact test, will be applied. For continuous variables the t-test procedure or the ANOVA, will be applied as appropriate. Non parametric ANOVA will be applied in case of ordinal data or not-normally distributed variables; the Dunnett test will be used as a posterior test. Treatment effect size will be calculated by dividing the difference between the baseline and the final visit value, by the standard deviation of the first visit value. Survival analysis with censored data will be used in order to evaluate time to remission and time to flare. Survival curves will be drawn with the Kaplan-Meyer method and compared with the log rank test. For multiple hypothesis testing, alpha level is set at 0.01. Emphasis will be placed on the intention-to-treat approach rather than on analysis of only the completers of the trial. All analysis will be done in a blinded manner.

Table: Time Oriented Table and duration time for each task

Task No	*Months*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	Personnel selection and training	■	■	■	■	■	■														
1	Translation of material		■	■																	
1	Data base and case report form development				■	■	■	■	■	■											
1	Submission to ethics committee				■	■	■	■	■	■	■	■	■								
2	Trials enrolment							■	■	■	■	■	■	■	■	■	■	■	■	■	■
3	Interim analysis																		■	■	■

Task No	*Months*	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
2	Trials enrolment	■	■	■	■	■	■	■	■	■	■										
2	Trial long term follow-up											■	■	■	■	■	■	■	■	■	■
3	Interim analysis											■	■	■							

Task No	*Months*	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
2	Trial long term follow-up	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
3	Final analysis															■	■	■	■	■	■

IMPORTANT: patients will be followed for a total of 5 years after enrolment to look at the 5 years mortality rate, and therefore the last patient will be out of the study at month 80.

Task No	*Months*	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
	Trial long term follow-up	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

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