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## 24th Newsletter - September 2016

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### News

#### **2016 PReS meeting in Genoa : the countdown has officially begun!**

Dear Friends,

There are just a few days left until Genoa will open its doors to all the participants of the **23rd PReS annual congress , from the 28th September to the 1st of October 2016 .**

The countdown has officially begun and we are looking forward to welcoming all of you!

**The PRINTO meeting** will be held on **Friday 30 September at 17.00-18.30** (following the PRES AGM meeting)!

#### **Agenda of the annual PRINTO General meeting (20th year Anniversary):**

- Introduction (A. Martini)
- Update on PRINTO Projects (N. Ruperto)
- MYPAN (P. Brogan)
- Pharmachild (N. Wulfraat, J. Swart, N. Ruperto)
- SHARE (P. Dolezalova, N. Wulfraat)
- The PRES EuroFever project (M. Gattorno, S. Federici)
- EPOCA/MAS studies (A. Ravelli, A. Consolaro, F. Minoia)

If you wish to have more info about the 2016 PReS meeting go to <http://www.pres.eu/pres2016/>

We are looking forward to welcoming you in Genoa,

Alberto Martini, President of PReS  
Nicola Ruperto, PRINTO senior scientist  
The PRINTO staff

### PharmaChild

Juvenile idiopathic arthritis (JIA) is the most common chronic paediatric rheumatic disease and an important cause of short and long-term disability and quality of life impairment. Methotrexate (MTX) is the second line agent of first choice for the treatment of children with polyarticular JIA who do not respond to NSAIDs.

Patients with JIA who do not respond or are intolerant to MTX are candidates for the treatment with biologic agents such as etanercept, infliximab, adalimumab, abatacept and others currently in development. However, little information exists on the long term safety of these agents that are currently being used in children with JIA.

Pharmachild is a pharmacovigilance project which aims at observing children with JIA for 3-10 years undergoing treatment with MTX or biologic agents in order to collect moderate, severe or serious adverse events occurred.

This project is conducted by the participating centres of the more than 50 countries belonging to the Paediatric Rheumatology International Trials Organisation ([PRINTO](#), certified ISO 9001-2008), or the Pediatric Rheumatology European Society ([PRES](#)). More than 200 PRINTO centres worldwide have already expressed their interest in participating in the project.

Pharmachild has been funded by the European Union (EU) within the FP7 framework (contract number 260353, principal investigator Dr Nico Wulfraat, co-principal investigator Dr Nicolino Ruperto).

The Pharmachild study has obtained the ENCePP Study Seal ([ENCePP](#)). The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) is a collaborative scientific network coordinated by the European Medicines Agency and developed in collaboration with European experts in the fields of pharmacoepidemiology and pharmacovigilance. The ENCePP Study Seal means that a study upholds high standards throughout the research process based on the principles of transparency and scientific independence.

#### At present...

Currently the PharmaChild registry includes the prospective data of nearly 3000 patients and the retrospective data of more than 8000 patients coming from more than 60 centres located in over 30 countries worldwide.

[See Enrollment table](#)

### COLLABORATION WITH PHARMACEUTICAL COMPANIES

The Pharmachild protocol envisages the opportunity of a cooperation with pharmaceutical companies, which may want to use the data derived from Pharmachild for regulatory post-marketing surveillance obligations related to their product towards regulatory authorities. In this cases, PRINTO will MAINTAIN THE OWNERSHIP OVER THE DATA COLLECTED in order to continue to fulfill the ENCePP principles of transparency and scientific independence. All related possible revenues will be totally reinvested for the research needs of the project to support the prolongation of the registry over the planned 3-10 years. List of companies which have agreed to cooperate with Pharmachild: - Bristol-Myers Squibb (Abatacept JIA Registry)

#### At present...

As of today the Abatacept JIA Registry sponsored by Bristol-Myers Squibb has enrolled 150 patients in the over 20 centres belonging to the PRCSG group in Canada and US and nearly 200 patients in the 30 centres belonging to the PRINTO network in Europe and rest of the world.

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### EPOCA

By involving the countries belonging to the network of PRINTO, EPOCA (EPidemiology, treatment and Outcome of Childhood Arthritis) aims to devise a new tool that enables the multidimensional assessment of the disease status in children with JIA. This new instrument, named Juvenile Arthritis Multidimensional Assessment Report (JAMAR), is simple easy to apply and multidimensional in nature. JAMAR's objectives are to foster the use of standardized quantitative outcome measures in daily care and to enable comparability of outcome data across different centers. Most clinical measures currently used to assess the disease status, particularly functional ability and health-related quality of life questionnaires, are lengthy and complex. According to agreed international guidelines JAMAR will be widely agreed upon and translated, cross-culturally adapted and validated in different languages by the PRINTO coordinators.

The Primary Objectives of the study are to translate, cross-culturally adapt and validate the JAMAR in the language of each participating countries and to compare the current outcomes of children with JIA across continents and countries.

The secondary objectives are connected with **Epidemiology** (to characterize and compare the frequency of the JIA categories in different countries and in different continents; to describe and compare the prevalence of iridocyclitis in different continents and in different countries; to define and compare the prevalence of ANA in the different JIA categories across diverse areas of the world); **Treatment** (to compare the treatments used in the management of children with JIA in different countries; to obtain information on the access to biologic medications in different countries; to compare the same outcomes by disease category); **Outcome** (to promote regular use of quantitative measures, either physician-centred or parent/patient-centred, in the assessment of children with JIA in standard clinical practice; to foster uniformity and standardization of clinical assessment of children with JIA across different countries).

### **At present...**

PRINTO is currently proceeding with the publication of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) supplement on a dedicated issue on parent/patient-reported outcomes (PROs) in juvenile idiopathic arthritis (JIA) in Rheumatology International. The supplement will contain one paper for each cross culturally adapted and validated version of the JAMAR (title example: The Italian version of the JAMAR, etc.) and a general introductory manuscript with the description of the methodological approach).

The authorship of each manuscript is defined according to PRINTO policy for authorship and the ICMJE criteria and completed with local input. The papers composing the supplement will be submitted this year.

**The EPOCA data collection has been completed by 43 countries and it is still on going in other 7. Globally, almost 9000 JIA patients and more than 4500 healthy controls from 128 centres in 50 countries have been currently collected and** confirmed through the dedicated online database. The statistical analysis and the paper drafting has been already completed by the PRINTO coordinating centre for 38 manuscripts.

**If you are interested in the project, please contact the PRINTO coordinating centre for the complete set of information (material for ethics committee submission, protocol, data collection forms).**

[See Enrollment table](#)

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### **ABIRISK**

The introduction of biopharmaceuticals (BPs) has been a critical step forward in the treatment of many severe diseases including juvenile idiopathic arthritis (JIA). There are now several BPs for the treatment of JIA. A major limitation to the use of BPs is the development of anti-drug antibodies in a subset of patients, that may decrease the efficacy of BPs by neutralizing them or modifying their clearance, and they may be associated with BP-specific hypersensitivity reactions. The prediction, prevention and cure of anti-drug immunogenicity are thus major goals in BP drug development and patient safety.

[ABIRISK](#) (Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Relevance to Minimize the Risk), whose enrollment ended on 31st March 2016, is a large European project funded by the [Innovative Medicines Initiative](#) (IMI) and it aims to provide an integrated approach to investigate anti-drug antibody formation in JIA, adult rheumatoid arthritis and other conditions treated with biopharmaceuticals, thanks to the cooperation of a large network of specialists and leading companies of [European Federation of Pharmaceutical Industries and Associations](#) (EFPIA).

PRINTO managed this project as a sub-study of PharmaChild and collected the biologic samples (Serum and RNA) of more than 120 children with JIA newly treated with adalimumab, etanercept or tocilizumab. The samples are going to be transferred to the PRINTO facilities in Genoa (Italy) soon, to be then distributed to the Abirisk consortium central laboratories who take care of the analysis. The clinical data are the data collected for the PharmaChild registry.

For further information, you can contact the [PRINTO](#) office.

Download [ABIRISK brochure](#).

[See Enrollment table](#)

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### **Eurofever Project**

The Eurofever project was promoted in 2008 by the work group of autoinflammatory diseases of the Paediatric Rheumatology European Society (PRES) and was supported by the Executive Agency for Health and Consumers (EAHC).

The general aims of the Eurofever project are to:

- sensitize pediatricians and pediatric rheumatologists to the prompt recognition of Autoinflammatory Diseases;
- provide proper information to families affected by these conditions;
- increase the knowledge on the clinical presentation, response to treatment and complications of these rare disorders.

The main objective of the project has been the creation of a registry of autoinflammatory diseases.

Last year a new section dedicated to Efficacy and Safety has been implemented and the registry is now able to collect also longitudinal information. New auto-inflammatory diseases have been added, as of today the following conditions are considered by the Project:

- Behçet disease

- Blau's syndrome/Early onset sarcoidosis
- Cryopyrin associated periodic syndrome
- Chronic recurrent multifocal osteomyelitis
- Deficiency of IL-1 receptor antagonist
- Familial Mediterranean Fever
- Mevalonate kinase deficiency (Hyper IgD syndrome)
- NLRP12 -associated periodic syndrome
- Pyogenic Sterile Arthritis, Pyoderma Gangrenosum and Acne (PAPA) syndrome
- Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)
- Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA)
- CANDLE syndrome
- DITRA syndrome
- Schnitzler syndrome
- Majeed syndrome
- Deficiency of Adenosine Deaminase 2 (DADA2)
- STING-associated vasculopathy with onset in infancy (SAVI)
- CARD14 mediated psoriasis (CAMPS)
- Undefined Periodic fever

**As of today 109 centres in 39 countries entered 3757 patients, 3015 with a baseline visit and 536 with also a follow-up visit.**

[See Enrollment table](#)

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### **SHARE Project**

The “Single Hub and Access point for paediatric Rheumatology in Europe” (acronym SHARE, project number 2011 1202; PI N. Wulffraat) aims to provide the European countries with recommendations for the care of children with rheumatic diseases. These recommendations are based on systematic literature reviews and on the surveys sent by PRINTO to individual centres belonging to its network all over the world.

To identify the specific needs for the optimal care in PRD, PRINTO implemented an online survey, available at [www.printo.it/SHARE](http://www.printo.it/SHARE) . In September 2016, more than 235 paediatric rheumatic centres had already completed the questionnaire.

Thanks to this project, PRINTO has updated and renovated its website for families, launched in 2003 (Ruperto N, et Al. for PRINTO/PRES Printo/Pres international website for families of children with rheumatic diseases: [www.pediatric-rheumatology.printo.it](http://www.pediatric-rheumatology.printo.it). Ann Rheum Dis 2005; 64:1101-1106).

**The new site [www.printo.it/pediatric-rheumatology](http://www.printo.it/pediatric-rheumatology) launched in December 2015, offers scientific information regarding the pediatric rheumatic diseases (PRD), the list of centres dealing with PRD, and the list of the family associations in more than 60 languages.**

The update of the disease information texts on paediatric rheumatic diseases has been performed with the help of several experts (paediatricians and healthcare professionals of the PRINTO/PReS network) and lay members of PRD family associations. Highly specialised working groups have been formed for the update of each specific disease text, whereas the parents' network ensured both reader-friendliness and completeness on everyday life and therapy issues. Afterwards, this final version has circulated among all the working group members for further reading and revision.

The updated English texts were then translated with the help of a professional agency in 14 languages (on the basis of national population and language diffusion). For all remaining languages, a translation process started with the involvement and volunteer contribution of all PRINTO/SHARE partners. The PRINTO national coordinators had the role to organize and lead the work process. To facilitate the translation process, the source texts in English were uploaded on a dedicated online platform implemented by PRINTO.

The new version of the website has been designed to adapt to the various portable devices, and allows all technical supports to browse easily among the contents – from a technical point of view, multimodality and user friendliness have been identified as the main characteristics to satisfy. Being a tool for families and patients, it includes customised illustrations created by professional illustrators, the possibility to share contents via the main social networks and a Search button (also available for voice search on smartphones), along with a map locating the centres and associations via Google Maps.

In order to ease the contents' consultation for the patients and their families, PRINTO has implemented an **APP for Android operating system** . Its design and structure reflect the website, with three main sections.

**Parent survey:** in order to mirror the WP4 survey for physicians and have a clear picture of the standards of care from a patient/parent point of view, a dedicated survey has been prepared in a collaborative effort between Dr Nico Wulffraat and the ENCA (European Network for Children with Arthritis) members. The patient/parent survey has been translated in the following languages: Arabic, Czech, Danish, Dutch, English, French, German, Greek, Hebrew, Italian, Latvian, Lithuanian, Polish, Portuguese, Serbian, Slovak, Slovenian, Spanish.

Currently, more than 630 patients have completed the SHARE parent Survey.

### The MYPAN trial

The MYPAN trial is an Open Label Randomised Controlled Trial of Mycophenolate Mofetil (MMF) Versus Cyclophosphamide (CYC) for the Induction of Remission of childhood PAN sponsored by University College London and coordinated by the Children Hospital in Liverpool and PRINTO (PI Dr P. Brogan). MYPAN will investigate the comparative efficacy and safety of MMF (experimental treatment) vs CYC (standard treatment) for induction of remission of childhood PAN. This will be the first ever randomized trial for childhood PAN. As of today 30 centres (UK and non-UK sites) have shown interest in participating in MYPAN: PRINTO is currently working at the submission procedures to the regulatory authorities and ethics committees of the non-UK centres, while the first patients have been enrolled at the UK sites. In occasion of the 2016 PReS meeting in Genoa, the study PI will give an update of the study during the PRINTO General Meeting on Friday 30<sup>th</sup> September 2016 from 5 pm, in the Maestrale Room.

### Patients enrolled in the PRINTO projects

Country	ABIRISK Registry	EPOCA	EUROFEVER	PHARMACHILD
Algeria	0	140	0	0
Argentina	0	473	57	123
Armenia	0	0	101	0
Australia	0	0	13	0
Austria	0	0	23	27
Belgium	0	200	13	0
Brazil	0	303	17	389
Bulgaria	0	300	0	57
Canada	0	253	8	0
Chile	0	119	5	0
China	0	0	14	0
Colombia	0	10	0	0
Croatia	0	200	11	100
Czech Republic	27	203	215	119
Denmark	0	402	135	542
Ecuador	0	18	0	11
Egypt	0	200	0	0
Estonia	0	210	0	0
Finland	0	247	0	0
France	17	222	284	291
Georgia	0	200	9	0
Germany	0	424	276	2
Greece	43	375	133	487
Hungary	0	297	24	126
India	0	375	3	119
Iran, Islamic Republic of	0	320	0	0
Israel	0	216	168	84

Italy	26	1400	1117	1352
Japan	0	0	6	0
Latvia	2	304	6	259
Lebanon	0	0	1	0
Libya	0	200	0	0
Lithuania	0	217	7	316
Mexico	0	199	0	12
Netherlands	0	317	112	619
Norway	4	375	0	359
Oman	0	143	6	16
Paraguay	0	151	0	0
Poland	3	248	9	29
Portugal	0	90	0	0
Romania	1	411	46	419
Russian Federation	0	24	61	461
Saudi Arabia	0	200	39	70
Serbia	0	349	5	276
Slovakia	1	208	1	126
Slovenia	0	223	13	53
South Africa	0	191	0	0
Spain	3	605	217	710
Sweden	0	144	1	0
Switzerland	1	100	94	490
Thailand	0	206	0	0
Turkey	10	525	205	1
Ukraine	0	200	0	0
United Kingdom	0	200	296	0
United States	0	413	6	0
<b>Total</b>	<b>138</b>	<b>13350</b>	<b>3757</b>	<b>8045</b>

### [PRINTO overall enrollment status](#)

#### [Latest PRINTO papers](#)

Ruperto N, Pistorio A, Ravelli A, Angioloni S, Martini A for the Paediatric Rheumatology International Trials Organisation (PRINTO).

#### **The PRINTO juvenile dermatomyositis trial – Authors’ reply.**

Lancet 2016;387:2600-2601. [PubMed](#)

Constantin T, Foeldvari I, Vojinovic J, Horneff G, Burgos-Vargas R, Nikishina I, Akikusa JD, Avcin T, Chaitow J, Koskova E, Lauwerys BR, Calvo Penades I, Flato B, Gamir ML, Huppertz HI, Raad JJ, Jarosova K, Anton J, Macku M, Otero Escalante WJ, Rutkowska-Sak L, Trauzeddel R, Velez-Sanchez PJ, Wouters C, Wajdula J, Zang C, Bukowski J, Woodworth D, Vlahos B, Martini A, Ruperto N for Paediatric Rheumatology International Trials Organisation (PRINTO).

#### **Two-year Efficacy and Safety of Etanercept in Pediatric Patients with Extended Oligoarthritis, Enthesitis-related Arthritis, or Psoriatic Arthritis.**

J Rheumatol 2016;43:816-824. [PubMed](#)

Grom AA, Ilowite NT, Pascual V, Brunner HI, Martini A, Lovell DJ, Ruperto N, Leon K, Lheritier K, Abrams K for the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG).

### **Canakinumab in Systemic Juvenile Idiopathic Arthritis: Impact on the Rate and Clinical Presentation of Macrophage Activation Syndrome.**

Arthritis Rheum 2016;68(1):218-28 [PubMed](#)

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Demirkaya E, Lanni S, Bovis F, Galasso R, Ravelli A, Palmisani E, Consolaro A, Pederzoli S, Marafon D, Simianer S, Martini A, Ruperto N, Pistorio A for the Paediatric Rheumatology International Trials Organisation (PRINTO)

### **A meta-analysis to estimate the placebo effect in juvenile idiopathic arthritis in randomized controlled trials.**

Arthritis Rheum 2016;68:1540-1550. [PubMed](#)

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Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, Aricò M, Avcin T, Behrens EM, De Benedetti F, Filipovich L, Grom AA, Henter J, Ilowite NT, Jordan MB, Khubchandani R, Kitoh T, Lehmborg K, Lovell DJ, Miettunen P, Nichols KE, Ozen S, Pachlopnick-Schmid J, Ramanan AV, Russo R, Schneider R, Sterba G, Uziel Y, Wallace C, Wouters C, Wulffraat N, Demirkaya E, Brunner HI, Martini A, Ruperto N, Cron RQ for the Pediatric Rheumatology International Trials Organization (PRINTO); the Childhood Arthritis & Rheumatology Research Alliance (CARRA); the Pediatric Rheumatology Collaborative Study Group (PRCSG); the Histiocyte Society.

### **Development and initial validation of classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis.**

Arthritis Rheumatol Arthritis Rheumatol 2016;68(3):566-76 [PubMed](#)

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Frid P, Nordal E, Bovis F, Giancane G, Larheim TA, Rygg M, Pires Marafon D, De Angelis D, Palmisani E, Murray KJ, Oliveira S, Simonini G, Corona F, Davidson J, Foster H, Steenks MH, Flato B, Zulian F, Baildam E, Saurenmann RK, Lahdenne P, Ravelli A, Martini A, Pistorio A, Ruperto N for the Paediatric Rheumatology International Trials Organisation (PRINTO).

### **Temporomandibular Joint Involvement is Associated with Quality of Life, Disability and High Disease Activity in Juvenile Idiopathic Arthritis.**

Arthritis Care Res [Epub ahead of print] [PubMed](#)

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Ter Haar NM, Jeyaratnam J, Lachmann HJ, Simon A, Brogan PA, Doglio M, Cattalini M, Anton J, Modesto C, Quartier P, Hoppenreijts E, Martino S, Insalaco A, Cantarini L, Lepore L, Alessio M, Calvo Penades I, Boros C, Consolini R, Rigante D, Russo R, Pachlopnick Schmid J, Lane T, Martini A, Ruperto N, Frenkel J, Gattorno M; Paediatric Rheumatology International Trials Organisation (PRINTO) and Eurofever Project.

### **The phenotype and genotype of mevalonate kinase deficiency: a series of 114 cases from the Eurofever Registry**

Arthritis Rheumatol [Epub ahead of print] [PubMed](#)

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## **Membership**

As of today, PRINTO has reached 1623 effective members in 582 centres from 82 countries.

If you wish to become a PRINTO member  
and receive regular updates about our research activity and invitations to our projects  
please go to:

<https://www.printo.it/contact/apply-membership>

Your cooperation will be more than welcome  
and your effort will be essential for the research in the field of paediatric rheumatic diseases.

**WELCOME ABOARD!**

## **PRINTO Advisory council & contacts**

### **Chairman**

**Alberto Martini, MD, Prof - Genoa, Italy**

### **Counsellors**

**Tadej Avcin, MD, MSc - Ljubljana, Slovenia**

**Michael Beresford, MD - Liverpool, UK**

Susan Nielsen, MD - København, Denmark  
Pierre Quartier, MD - Paris, France  
Claudia Saad Magalhães, MD, PhD - Botucatu, Brazil  
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