Drugs for….

PaediatRic Onset MultIple SclErosis (PROMISE)

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Rome, January 14th, 2018

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A multi-centre, open-label, randomized, pragmatic clinical trial, embedded within everyday clinical practice, aimed to compare the effectiveness and safety of two treatments (interferon-beta 1a 30 mcg weekly i.m. and glatiramer-acetate 40 mg every other day s.c.) for paediatric patients affected by Multiple Sclerosis (POMS)

funded by the Italian Drug Agency (AIFA)

Agenzia Italiana del Farmaco
AIFA

Il Direttore Generale

Roma, 27/10/2017

Oggetto: Comunicazione relativa al Bando AIFA 2016 Ricerca Indipendente

Egregia prof.ssa Margari,
sono lieto di comunicarLe che, sulla base del punteggio ottenuto in seguito alla valutazione dei protocolli di studio del Bando AIFA 2016 Ricerca Indipendente sui Farmaci, il Consiglio di Amministrazione dell'AIFA del 14 settembre u.s. ha approvato il finanziamento della Sua proposta identificata con codice AIFA-2016-02365052 dal titolo "Multi-centre, randomised, open label pragmatic trial to compare the effectiveness and safety of interferon-beta 1a (IFN-beta 1a) weekly i.m. and glatiramer-acetate (GA) in paediatric patients affected by multiple sclerosis".

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Background

- Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the Central Nervous System that usually affects young adults and represents one of the major cause of disability in this population.
- Paediatric onset (before 18 years) MS (POMS) represents 3-5% of total MS population.
- POMS is a rare disease with an estimated annual incidence ranging between 0.13 and 0.6 /100.000 and with a more severe prognosis compared to adult-onset MS (AOMS).
- It remains a challenging condition to treat because of the highly inflammatory nature of the disease (higher relapse rate and MRI lesion accrual compared to AOMS), the prominent cognitive issues.
- POMS reach severe disability at a younger age than AOMS

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Ghezzi A, Neurology 2016; Simone M, Curr Treat Options Neurol 2016

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Background

- Many disease-modifying therapies are currently available for adults with relapsing-remitting MS (RRMS)
- No medication currently approved for adults with RRMS has completed testing for pediatric MS in randomized placebo-controlled trials (RCTs), although several pediatric MS trials have recently been launched.
- To date, interferon-beta and glatiramer acetate are the most commonly used first-line treatments in children, although the efficacy and safety of these drugs have only been studied in observational cohorts and in very small unblinded RCts.
  - Comparative effectiveness and safety between these two DMTs has never been assessed in POMS
  - Thus which is the best injectable therapy for controlling disease activity and progression in treatment-naïve POMS is yet not known

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Pragmatic Clinical Trial

PCT is the best method to answer questions:

- Can an intervention actually work in real life?
- Which intervention is most effective?

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Pragmatic Clinical Trial

(Large Scale RCT)

- **Randomization**
- **Data collection occurs in routine practice settings**
- Broad inclusion criteria
- Large and diverse patient populations
- Active comparator of the same or different class (usual care)
- Endpoints: patient-oriented and major clinical outcomes (i.e. patient symptoms, QoL and costs)
    - **Large External Validity**

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Objectives

Primary objective is to compare the effectiveness of IFN beta 1a (30 mcg weekly i.m.) and GA (40 mg every other day s.c.) in POMS, in order to demonstrate their equivalence or the superiority of one of them on clinical and MRI outcomes.

Secondary objective is to compare safety and cost-effectiveness of the two drugs.

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Study Population

Inclusion criteria

- Diagnosis of POMS (Krupp L, 2013)
- Children and adolescents aged 10 to 17 years**;**
- Relapsing remitting course;
- At least one MS relapse during the previous year;
- EDSS score of 0 to 5.5

Exclusion criteria:

- Patients with progressive MS;
- Patients with an active, chronic disease of the immune system other than MS;
- Patients meeting the definition of Acute Disseminated Encephalomyelitis (ADEM);
- Patients with thyroid dysfunction;
- Patients with severe renal insufficiency.

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Study Design (1)

- **Study type**: multi-center, open labe,l randomised pragmatic trial

- **Centralized randomization:** Subjects will be randomized to receive GA (Copaxone) or IFN-beta-1a (Avonex) in a 1:1 ratio and stratified according to 3 age groups (10 to <12 years, 12 to <15 years, and 15 to <18 years)

- **Duration**: 36 months
  Anticipated Study Start Date: February 2018
  Estimated Study Completion Date: May 30, 2021

The study consists of 2 phases:

- **a pre-randomization screening phase:** eligibility for the study is confirmed and informed consent is signed
- **a treatment phase:** on Day 1 eligible patients will be randomized to one of the two treatment arms. Post-randomization visits are scheduled at 2 weeks, 6 months and then every 6 months during the treatment phase.

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Study Design (2)

- **Clinical evaluation will be performed at baseline and every six months:** complete medical history, **physical and neurological examination**, with **disability assessed by the Expanded Disability Status Scale (EDSS),** annualised **relapse rate**, **Quality of life** measured by the Pediatric Quality of Life (PQoL) scale, **Fatigue** assessed by the Modified Fatigue Impact Scale (MFIS), vital signs, **haematological/blood chemistry, urinalysis and pregnancy test.**

- **Brain MRI scan (by 1.5 T MRI) and cognitive and behavioural evaluation will be assessed at baseline and every 12 months.** Prior to the start of the study, the neuroradiologist and MRI technician from each centre will receive an MRI Manual, outlining technical implementation, image quality requirements and MRI administrative procedures. Cognitive and behavioural evaluation will be assessed using the **Symbol Digit Modalities Test (SDMT)**

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Endpoints

Primary endpoint

- Proportion of subjects free of new or newly enlarging T2 hyperintense lesions on brain **MRI scans** at 96 months.

Secondary endpoints

- **Annualized relapse rate** (ARR) at weeks 48 and 96;
- Proportion of subjects free of relapse up to Week 96;
- Time to first relapse;
- **Time to disability progression** defined as 1 point increase of the Expanded disability Status Scale (EDSS) score confirmed at 6 months;
- Number of new or newly enlarging T2 hyperintense lesions on brain MRI scans at Weeks 48 and 96;
- Number of MRI T1Gd-enhancing lesions on brain MRI scans at Weeks 48 and 96;
- **Change of Symbol Digit Modality test (SDMT**) at Weeks 48 and 96;
- **Change of Fatigue** (FS) score at Weeks 48 and 96;
- **Change of QOL** (ped QOL) evaluated through Patient Reported Outcomes (PROs) at Weeks 48 and 96;
- **Frequency and type of Adverse Events (AEs).**
- **Cost-efficacy analyses**.

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- **Coordinating Centre**: Childhood and Adolescence Neuropsychiatry Unit at Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Italy

- **Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF)** will be in charge of monitoring and data analysis and other requirements for the clinical trial in accordance with GCP

- **Fondazione Italiana Sclerosi Multipla (FISM) and Associazione Italiana Sclerosi Multipla (AISM) (**responsible with the University of Bari of the Italian MS Registry containing > 40.000 patients) will provide list and contacts of recruitment pediatric MS centers

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List of participating Centers

1. Centro Sclerosi Multipla, Università Bari; Responsabile M. Trojano
2. Centro Sclerosi Multipla - Neurologia Universitaria Foggia; Responsabile C. Avolio
3. U.O. Neuropsichiatria Infantile, Policlinico di Sassari; S. Sotgiu
4. Centro Sclerosi Multipla - AOL Policlinico Vittorio Emanuele – Univ. di Catania; Responsabile F. Patti
5. S.C.D.U. di Neurologia 1 - Centro di Riferimento Regionale per la SM - Neurologia 2 - Ospedale S. Luigi Gonzaga Orbassano; Responsabile A. Bertolotto
6. Divisione di Neurologia - Ospedale Pediatrico Bambino Gesù – Roma; responsabile F. Vigevano.
7. Unità semplice funzioni speciali epilessia dell'infanzia e dell'adolescenza, IRCCS Mondino – Univ. PV; P. Veggiotti
8. U. O. C. di Neurologia Ped. - Az. Ospedaliero-Universitaria di Padova; Dott.ssa A. Suppiej
9. Dipartimento di Neuroscienze, Ospedale Pediatrico A. Meyer-Univ. di Firenze; R. Guerrini
10. Centro Malattie Demielinizzanti - SOD Neurologia 1 – AOU Careggi – Firenze; MP. Amato
11. Centro Regionale per la diagnosi e la cura della Sclerosi Multipla ASL8, Università di Cagliari;E. Cocco
12. Centro Clinico per la Sclerosi Multipla, II Clinica Neurologica, Seconda Università di Napoli - Clinica Neurologica. Responsabile G. Lus.
13. Centro Provinciale Sclerosi Multipla - AOU Policlinico Federico II Napoli; V. Brescia Morra
14. Centro Sclerosi Multipla - Ospedale San Raffaele Milano; G. Comi
15. Centro per la Diagnosi e Cura della Sclerosi Multipla e delle Malattie Demielinizzanti - Università di Palermo; Responsabile: G. Salemi
16. S.S. Sclerosi Multipla dell'IRCCS Fondazione Istituto Neurologico Nazionale C.Mondino – Pavia. Responsabile: R. Bergamaschi.
17. Neurologia 2 - Centro Studi SM - Ospedale di Gallarate; Responsabile M. Zaffaroni/A. Ghezzi
18. Centro Clinico Policlinico Umberto I - Università di Roma Sapienza. Responsabile: E. Millefiorini-
19. Centro Sclerosi Multipla P.O. "Madonna delle Grazie"Matera; Responsabile MG. Coniglio
20. Università La Sapienza Ospedale S. Andrea – Roma Centro SM; Responsabile C. Pozzilli.

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Sample size

The estimated sample size, primarily based on feasibility, is of approx 50 subjects, at the 96-week time point, for each treatment group.

Based on an estimated dropout rate of approximately 30% over 2 years:

a total of 142 subjects should be enrolled to have at least 100 evaluable subjects (50 subjects/treatment group).

…but POMS is rare, …thus we are looking for the collaboration of other MS centers to achieve this goal

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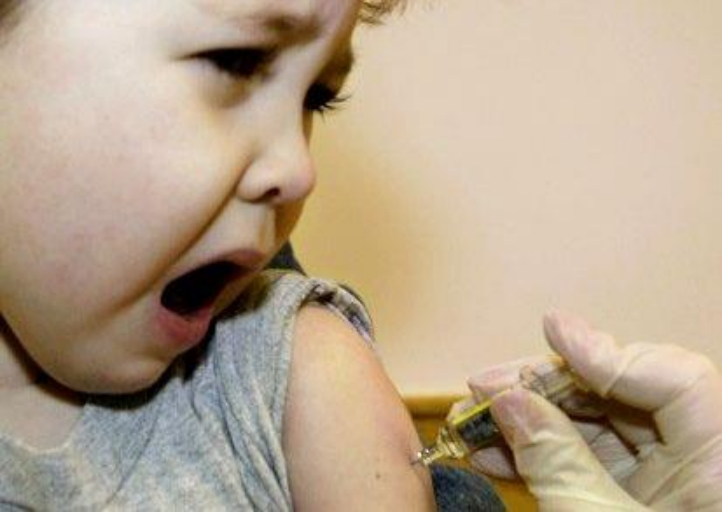
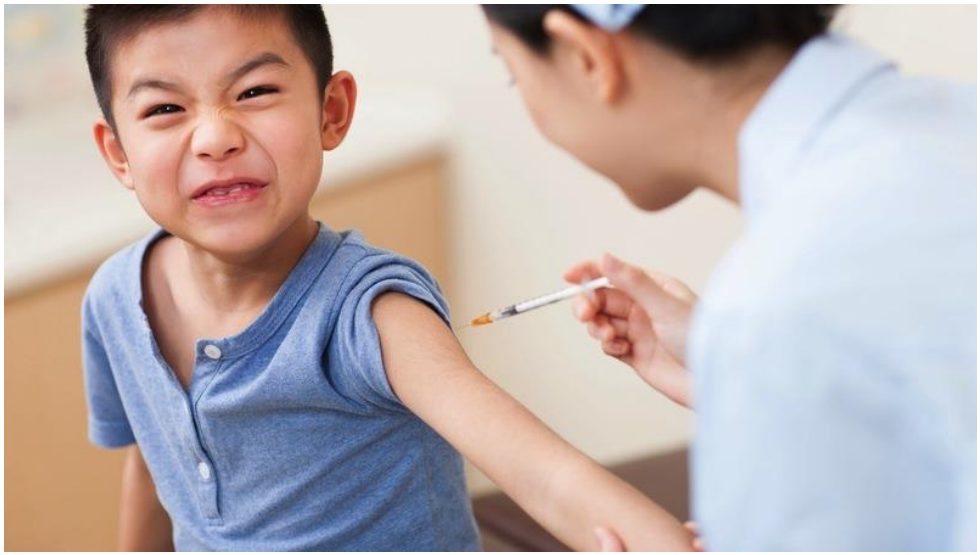


THANK YOU FOR YOUR ATTENTION!!!!!



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