Full Proposal Application Form

1.a Project Title: Rare disease: use of clinical trial simulation for the choice and optimization of study design

1.b Project acronym: CRESim

1.c Project submitted in Theme A "Methodology"

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4. **Total funding applied for:** 991 300 €

5. **Project duration:** 36 months

Please note that some funding agencies limited the budget for researchers from these countries. It is recommended that applicants will check the national eligibility criteria and consult the respective national contact person. See the call text on www.PRIOMEDCHILD.eu section Joint Call.

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6. Scientific abstract of the project

Background: Rare diseases are defined based on their low incidence, less than one in 2,000. Whereas randomized controlled trials (RCTs) are currently the gold standard for drug evaluation, there is still no general validated approach for the assessment of (orphan) drugs in this field.

Objectives of the CRESim ('Child-Rare-Euro-Simulation') project: To develop a platform performing trial modelling and simulation in order to identify optimal trial designs in children for the evaluation of (orphan) drugs tailored to different types of rare diseases.

Methods: *In silico* approach using RCT modelling and Monte Carlo simulation, implemented for different categories of rare diseases in pediatrics. Several RCTs with different experimental designs will be modelled and simulated, and the different designs will be compared in terms of *trial duration* and *precision* of the estimation of the treatment effect.

Expected outcomes: Improvement and optimization of the development of new orphan drugs.

Dissemination of results: Dissemination will target those involved in drug development (i.e. pharmacologists, therapeutic specialists, methodologists and statisticians), and in drug registration (public health decision makers), and registration authorities (EMEA and national agencies).

7. Keywords:

Rare diseases, orphan drugs, modelling, clinical trial simulation, experimental designs, pharmacokinetic-pharmacodynamic relations

8. Project description

Introduction

Rare diseases: a new Public Health concept

The European Commission on Public Health defines rare diseases as 'life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them.' The term low prevalence is defined as less than 1 in 2,000 persons. It is estimated that between *5,000 and 8,000 distinct rare diseases* exist today, affecting 6% to 8% of the population, 24 to 36 million people in the European Community. 80% of rare diseases have identified *genetic origins*, others result from *infections*, *allergies* or are due to *degenerative* and *proliferative* causes. Rare diseases are characterized by a *broad diversity* of disorders and symptoms across diseases and also across patients suffering from the same disease. Therefore, it is impossible to develop a Public Health policy specific to each rare disease. A *global approach to rare diseases* is consequently required for establishing policies dealing with scientific and biomedical research, drug research and development, industry policy, training, social benefits, hospitalization and outpatient treatment.

Orphan medicines

An orphan drug is a pharmaceutical agent specifically developed to treat a rare medical condition, referred to as an orphan disease. Orphan drugs follow the same regulatory development path as other pharmaceutical products, with studies focusing on pharmacokinetics, pharmacodynamics, dosing, stability, safety and efficacy. However, some statistical burdens are lessened in an effort to maintain development momentum. For example, orphan drug regulation generally acknowledges that it may not be possible to test 1,000 patients in a phase III clinical trial, given the number of afflicted persons.

The standard approach to clinical trials and a need for alternatives

Even though the available population of potential research participants does not allow the conduct of adequately powered randomized clinical trials (RCTs), there is a need for facilitating the development and availability of high quality, ethically researched, and appropriately authorized medicines in pediatric rare diseases, without subjecting children to unnecessary trials. Historically, drug developers and federal regulators have been worried of small clinical trials, primarily because of their low statistical power and generalizability. New approaches to protocol design are presently needed for trials with small sample sizes that can assess the potential therapeutic efficacy of drugs, biologics, devices, and other medical interventions.

8.1 Objectives of the Project

8.1.1 Main and secondary objectives

The main objective of the **CRESim ('Child-Rare-Euro-Simulation') project** is to create a platform for performing *in silico* experiments assessing designs of RCTs for drug evaluation in children with rare diseases. For demonstration purposes, three diseases are considered: severe myoclonic epilepsy in

infancy (Dravet Syndrome, DS), cystic fibrosis (CF) and lymphoblastic lymphoma (LL). For each disease, several virtual RCTs will be simulated using different experimental designs and the results will be compared in terms of *trial duration* (for the patient, the investigator and the sponsor) and *precision of the estimation of the treatment effect*.

8.1.2 The innovative potential of the expected results

An important goal of clinical trial simulation is to develop well-designed protocols that will maximize the ability to address the stated aim(s) of a proposed clinical trial, i.e. the quantification of the potential therapeutic efficacy of drugs. Such an *in silico* approach has never been widely applied neither in the field of RCTs designs nor for orphan drug evaluation.

8.1.3 Scientific impact

The project will provide a new environment for more effective healthcare, i.e. an *in silico* platform for RCTs simulation in rare diseases. This will allow to investigate new compounds for treating rare diseases with the following advantages: i) reduction of human experimentation in children by simulating the effect of the compound before starting any clinical trial, ii) reduction of time and expenses on unsuccessful drug clinical trials, and iii) *in fine* stimulation of the orphan-drug development process in pharmaceutical industry.

8.2 Background and present state of the art in the research field and rationale of project

8.2.1 RCTs in rare diseases

The most common clinical trial design is the *parallel-group design*, in which participants are randomized to one of two or more arms, active control(s) or a placebo. Alternative designs (Evans and Ildstad, 2003) have been used for small clinical trials: crossover, factorial, randomized withdrawal and early-escape designs.

The *crossover design* compares two or more interventions by randomly assigning each participant to receive the interventions being tested in a different sequence. Once one intervention is completed, participants are switched to another intervention.

In a *factorial design*, two or more treatments are evaluated simultaneously with the same participant population through randomization in various combinations of the treatments.

In a *withdrawal design*, individuals who respond positively to an experimental intervention are randomized to continue receiving that intervention or to receive a placebo.

The *early-escape design* is another way to minimize an individual's duration of exposure to a placebo: participants are removed from the study if they fail to respond to a defined extent.

Some trial designs have been especially developed for small size studies, including: single subject (*n*-of-1), sequential, and adaptive designs.

A *N-of-1* trial design is a randomized multi-crossover study of an individual patient's responses to a set of (often two) treatments. Treatments are randomly assigned individually or within paired periods

and blindly applied to a patient. At set time intervals, corresponding to these different treatment periods, measurements of the patient's disease status are taken. After several crossover periods, comparisons of the outcomes obtained during the periods for the (two) drugs are made.

In a *sequential* design, participants are sequentially enrolled in the study and are assigned a treatment (usually at random). The probabilities that participants will be assigned to any particular treatment are modified as they become available. The aim is to improve the efficiency, safety, or efficacy of the experiment while in progress by changing the rules of treatment allocation.

An *adaptive* design seeks to skew assignment probabilities to favor the better-performing treatment in a trial that is under way. A major advantage of adaptive design (e.g. 'play the winner' rule) is that over time more patients will be assigned to the more successful treatment.

The *Bayesian approach* is suited to adapting to information that accrues during a trial, potentially allowing for smaller more informative trials and for patients to receive better treatment. Accumulating results can be assessed at any time, including continually, with the possibility of modifying the design of the trial, for example, by slowing (or stopping) or expanding accrual, imbalancing randomization to favor better-performing therapies, dropping or adding treatment arms, and changing the trial population to focus on patient subsets that are responding better to the experimental therapies.

Multi stage designs will be also simulated especially for phase II clinical trials.

Lastly, *the meta-analytic approach* will be also considered.

8.2.2 Clinical trials modelling and simulation

In silico simulations (Boissel et al, 2005) have become a powerful tool for the researcher. Simulation consists in building a virtual model of reality in order to perform experiments by changing the values of the model parameters. RCT simulations can be defined as the generation of a treatment effect for a virtual patient obtained by modeling trial design, human behavior, disease progress and drug effects using numerical methods and specific mathematical models (e.g. pharmacokinetic and pharmacokinetic-pharmacodynamic models for drug behavior and effect).

The CRESim project belongs to the framework of an *in silico approach*, with the use of *RCT modelling* and *Monte Carlo simulation* (Kimko and Duffull, 2003) in order to evaluate and compare various clinical trial designs in different rare diseases.

8.3 Work plan highlighting the originality, novelty and feasibility

8.3.1 Aims

Various experimental designs will be modelled and simulated for each considered disease for comparison purpose in terms of : i) *trial duration*, this criterion represents the 'burden' of the trial for the patient, the investigator and the sponsor, and ii) *precision of the estimation of the treatment effect*, a criterion evaluating the 'performance' of the trial.

8.3.2 Methodology

Modelling *in silico* trials requires mathematical models for representing the disease, the drug / patient interaction, and the experimental design (Chabaud et al, 2002). Such models already exist and are published, but they usually address a restricted aspect of the problem, e.g. PK and PK/PD models in adults for a given drug, pathophysiology and evolution of the disease (such as receptor function, biomarker action, and genetic aspects). Published models will be primarily searched for in bibliographic data bases. However, additional models will be specifically developed.

Simulating clinical trials requires to set-up a *simulation plan*, detailing a series of linked models (Bajard et al, 2009, Blesius et al, 2006). Each simulation model is categorized into one of three sub models:

- the input-output (IO) sub-model predicts outcomes for each patient. It includes a pathophysiological model of the disease if any, and the PK-PD drug properties (Nony and Boissel, 2002). The model structure and parameters must be based on existing data from clinical studies, to adequately reproduce the reality regarding drug (and metabolite) concentrations, biomarkers of therapeutic or toxicological response, or the incidence of a clinical outcome (e.g. death, occurrence of a seizure or improvement in cognitive scales in epilepsy) or an adverse event (Wang et al, 2009, Duffull et al, 2000).
- the covariate distribution sub-model describes the characteristics of the patients and is built from existing patient databases;
- the execution submodel describes the characteristics of experimental design and of protocol deviations (i.e. deviation(s) from the protocol either patient-related or investigator-related) (Bajard et al, 2009). All protocol deviations are unexpected by nature, and therefore only probabilistic models can be used to simulate them (Nony et al, 1998).

The full model will express the quantitative therapeutic effect as the sum of the IO sub-model and the execution sub-model (Boissel et al, 2008).

Simulation process. In each disease, the simulation process proceeds in two steps: the simulation of a virtual population of patients, and the simulation of RCTs following specific experimental designs.

Simulation of a virtual population. A population of 'N' virtual patients will be generated. Several covariate values will be attributed randomly to each patient, : parameters of the IO submodel, both for therapeutic and for adverse effects, parameters of the execution submodel, and covariates characterizing investigator (center) or patient (inclusion/exclusion criteria, baseline characteristics). Samples of patients will be randomly drawn from this population for inclusion in each further clinical trial.

Simulation of RCTs. Random samples of patients drawn from the virtual population will be included in *in silico* clinical trials. Where appropriate, random treatment allocation is based on series of random-permutation blocks in order to avoid imbalance between the treated and control groups for each trial.

The diversity of drug-patient interactions will be simulated using the variance of each parameter distribution of the IO sub-model, both for therapeutic and adverse effects. The 'true' treatment effect (e.g. true odds-ratio-OR-) will be calculated as follows: patients will be successively considered as treated and as untreated, and the two corresponding odds will be calculated (each odds corresponding to the ratio between the number of patients without and with a given clinical event). The "true" OR will be then obtained by calculating the ratio of the two odds. Some protocol deviations might be added to the full model, either treatment related (e.g.. switch to another treatment) or patient related (e.g., missed visit, definitive dropout). Thus in one disease, a given number (e.g. 100 to 200) of virtual trials will be simulated independently for each experimental design.

Statistical analysis of each RCT results. Depending on each study design, different statistical methods will be considered such as parametric and/or non parametric tests, hierarchical models, sequential analysis (e.g. use of a triangular test), and / or meta-analytical techniques.

Analysis of final results. The final analysis must determine the most appropriate design for a given pair 'disease-drug'. This analysis will be descriptive. For each situation, i.e. [trial design, pair 'rare disease-drug'], the number of times each trial result appears significant (significance level: 5%) will be considered for the final hierarchy. The final hierarchy will be presented taking into account both the precision of the estimation of the treatment effect (cf. above), and the trial duration.

Example: comparison between cross-over and parallel group designs

The time duration of cross-over and parallel group trials (Senn S, 1993)

Let us suppose that 2p and 2c patients are included respectively in a parallel and a cross-over study. Randomization takes place just before treatment begins and each treatment period is t time units long. For the cross-over there is a wash-out period of length w between periods of therapy, where w might be zero. We assume that: i) a single measurement is taken at the end of each treatment period, and that ii) the effect of the first treatment has disappeared when the second period endpoint measurement is done. Suppose also that the time between recruitment of individual patients is r_1 for the parallel and r_2 for the cross-over. Further suppose that the time spent in the trial before randomization, including, any pre-randomization visits is v (we shall refer to this period as the *run-in).* The various time durations comparing for cross-over and parallel group designs are given below:

	Parallel	Cross-over
Time that each patient spends in the trial	$v + t$	$v + 2t + w$
Total investigation time	$2p\ (v + t)$	$2c\ (v + 2t + w)$
Total trial time	$2pr_1 + v + t$	$2cr_2 + v + 2t + w$

This model is a considerable simplification, and should only be considered as a starting example. In many cross-over trials *w* is not fixed and a minimum value is specified. What constitutes an appropriate value for *t* will have to be decided by the investigator. The recruitment periods r_1 and r_2 are not known in advance and variable within trials. On average r_2 will be greater than r_1 since the inconvenience for patients is greater in the cross-over trial, making patient inclusion more difficult. Some relevant time durations may also be calculated using this model :

- The extra time each patient spends in the trial in the cross-over compared to the parallel is $t + w$. or the time of one treatment plus the time of a wash-out ;
- The total investigation time for the cross-over will be less than that for the parallel providing :

$$p > [1 + (t + w) / (t + v)] c$$

- The total trial time for the cross-over will be less than that for the parallel providing :

$$p > cr_2 / r_1 + (t + w) / (2r_1)$$

The precision of cross-over and parallel group trials

In order to consider the precision of the results of the two trials, we need to introduce a specific model. We assume that there is no carry-over and consider patient effects as random. If we let the response on patient i in group *h* (h = 1 or 2) and period *t* (*t* = 1 for the parallel, = 1 or 2 for the cross-over), be Y_{iht} , then we may write : $Y_{iht} = E(Y_{iht}) + \beta_{ih} + \varepsilon_{iht}$,

where β_{ih}, is the effect due to patient i in group *h* (a 'between-patient error', now considered random) and ε_{iht} is a disturbance term (a 'within-patient' error). We also assume $E(\beta_{ih}) = 0$, from which $E(\varepsilon_{iht}) = 0$, and that $var(\beta_{ih}) = \sigma_h^2$ and $var(\varepsilon_{iht}) = \sigma_w^2$. We assume in addition that β_{ih} and ε_{iht} are independent, from which it follows that their covariance is zero and that all ε_{iht} are independent of each other. If we denote the four cells means of a cross over by $\tilde{Y}_{.11}$, $\tilde{Y}_{.12}$, $\tilde{Y}_{.21}$, $\tilde{Y}_{.22}$, then the *CROS* estimator (i.e. the standard estimator of the treatment effect for the *AB/ BA* crossover) is:

$$CROS = [\{\bar{Y}_{.11} - \bar{Y}_{.12}\} + \{\bar{Y}_{.22} - \bar{Y}_{.21}\}]/2.$$

Then we obtain the following expression for the variance: **var (CROS) = σ_w^2 / c**

On the other hand for the parallel we use the first periods only and hence the estimator of the treatment effect PAR is:

$$PAR = \bar{Y}_{.11} - \bar{Y}_{.21}$$

Applying our rules for linear combinations, we obtain: **var (PAR) = 2 ($\sigma_b^2 + \sigma_w^2$) / p**

If we now consider how many patients we have to recruit to the parallel to have the same variance of the *PAR* estimator as for the *CROS* estimator in the cross-over.

We thus obtain: $2 (\sigma_b^2 + \sigma_w^2) / p = \sigma_w^2 / c$, from which we have: $p = 2c (\sigma_b^2 + \sigma_w^2) / \sigma_w^2$

General implementation. Because of the complexity of the models and designs considered in our project, the above mentioned analytical approach will not be possible in most situations. This explains why we will use a Monte Carlo approach for the quantification of the precision of the treatment effect. X experimental designs of RCT will be identified, and Y categories of pairs [rare disease, drug] will be considered. A specific mathematical model will be built for each experimental design and for each pair [rare disease, drug]. X*Y simulations will be performed in order to investigate in each case the precision of the treatment effect estimate. The duration of each trial will be calculated analytically, considering the patient, the investigator and the sponsor levels.

Clinical situations of interest. These situations have been chosen for demonstration purpose, i) to cover a wide range of diseases with a variety of symptoms/ evolution profile / type of treatments; ii) to involve partners interested in modelling and clinical research, who are highly recognized in their domain, and have access to databases which are needed for model set-up and testing.

Epilepsy. Dravet syndrome (DS) is an epileptic encephalopathy, starting in the first year of life and characterized by febrile and afebrile, generalized and unilateral, clonic or tonic-clonic seizures.

Available databases: Partners involved in the project have a recognized expertise in meta-analysis of individual patient data (Kassai et al, 2008), stiripentol evaluation in DS and have run a PK population study (Chiron et al, 2000, Guerrini and Pons, 2000). A database of 80 patients (30 years of follow-up) is available at the Meyer's Hospital. In a recent study (Drs. Dravet and Guerrini), 25 new onset patients have been enrolled to monitor the expression of epilepsy.

Cystic fibrosis (CF). This most common life-shortening inherited disease is caused by a defective CF transmembrane conductance regulator gene, lung disease being the primary cause of death. Spirometry, considered the gold standard to monitor CF lung disease and still required by regulatory agencies as primary end point in RCTs, is inadequate early in the disease process and has become insensitive to monitor disease progression. Computed tomography (CT) was shown to be more accurate and precise than spirometry. Composite scores that include spirometry and CT components might also allow performing small size trials (Tiddens and Brody, 2007, Tiddens and de Jong, 2007).

Available databases: The 'ErasmusMC' clinical database includes lung function, CT and other key follow-up data of all CF patients collected since 1996, i.e. 150 children routinely monitored, over 6500 patient encounters. The 'Severe Advanced Lung Disease (SALD) database' contains spirometry and CT data and survival date of over 500 lung transplant patients from 17 lung transplant centers. The European registry (15000 patients) in which the ErasmusMC CF center participates, and the Epidemiologic Study of CF registry containing long term longitudinal data on 25.000 patients can be available. Datasets of 4 RCTs in ErasmusMC plus two studies (completion by mid April 2010) will be also available.

Lymphoblastic lymphoma (LBL) . Lymphoblastic lymphoma (LBL) accounts for 20-25 % of the Non Hodgkin lymphoma of childhood and adolescence. The vast majority are T-cell-lymphoblastic lymphoma (T-LBL). A major problem is the dismal prognosis of individuals with T-LBL failing first line therapy. Efforts have to be undertaken to induce and maintain disease response without early relapse (Uyttebroeck et al, 2008). Because of the relatively low incidence of the disease, a number of national European cooperative study groups have co-operated in optimizing the treatment and investigating the disease (participating groups : AIEOP (Italy), BFM (Austria, Czechia, Germany, Switzerland), CoALL (Germany), DCOG (Netherlands), EORTC (France, Belgium), NOPHO (Norway, Sweden, Finland, Denmark, Iceland), PPLLSG (Poland), Spain, SFCE (France) and UKCCSG, (United Kingdom)).

Available databases: The HCL (Hospices Civils de Lyon) is currently running the French part of the study EURO-LB 02, an international multicentre cooperative study. The corresponding database includes more than 80 T- LBL cases, with a cohort treated with standard treatment, and data from a clinical trial with 4 treatment arms.

8.3.3 Work package structure and involvement of research partner in each work package

The project will include seven workpackages.

WP1– Methodology, scientific coordination and management (P. Nony, C. Cornu, B. Kassai, Lyon, FRANCE): The methodological aspects will include up-date bibliographic search for available experimental designs and the definition of the characteristics used in the simulation process (e.g. choice of a virtual population of pediatric patients, modelling of various RCTs with specific designs). In addition, a flexible management structure will be created within CRESim, taking into account the complexity of developing models and implementing these models *in numero*.

WP2 to 4–: For each WP, the work will consist in i) Description of the disease(s) for modelling purposes: bibliographic search for existing discursive and mathematical models, pathophysiology of the disease (and some of its specific pediatric syndromes), epidemiological studies describing the natural history of the disease, spontaneous morbidity and mortality, and time to occurrence of a clinical event which could be considered as an endpoint in a RCT. ii) Description of existing treatments or care, evolution under treatment; existing databases will also be useful for description purposes. iii) Providing patient databases and/or RCT databases available in each WP team in order to validate the models considered for further RCT simulation in the project.

These WP partners will also have to participate in the choice of modelling options. After simulations have been performed, they will also contribute in results interpretation.

In this application, one example of disease is shown for each WP, but other diseases or syndromes in the same medical domain will also be used: WP2- Epilepsy (R. Guerrini, Florence, ITALY), WP3- Cystic fibrosis (H. Tiddens, Rotterdam, NL), WP4- Hemato-oncology (Y. Bertrand, Lyon, FRANCE).

WP5– Modelling (L. Aarons, Manchester, UK): this WP includes modelling diseases (in collaboration with WP 2 to 4): i) bibliographic review; ii) analysis of the characteristics and properties of the mechanistic / mathematical models dealing with: pathophysiology, pharmacokinetics, pharmacokinetic-pharmacodynamic relations and iii) modelling the probability of occurrence of a given clinical endpoint for the diseases and drugs chosen as examples. iv) in collaboration with WP1 modelling and implementation of specific RCT designs; v) in collaboration with WP 2 to 4, the disease and/or therapeutic models will be validated using available databases of real patients.

WP6– RCTs simulation and statistical analysis (S. Chabaud, D. Perol, Lyon, FRANCE): This project requires a consistent and reliable modelling methodology which is expected to be reusable for any given rare disease of interest. The main challenge for WP6 is to build a flexible architecture allowing: i) accumulated knowledge from WP2 to 5 to be incorporated in a seamless fashion in the models along the project life and ii) mathematical solutions and models to be easily reused in the context of future research projects. The overall modelling framework will be based on two major principles : i) piecemeal achievement with each sub-model having clearly identified inputs and outputs that can be used to validate the global model i.e. the *'Lego®-like' principle*; ii) possible replacement of any submodel by a more detailed one, i.e. the *'plug-in'* principle.

WP7– Dissemination and exploitation (G. Pons, F. Dufour, Paris, FRANCE): A collaborative web-based platform will represent the core instrument for networking activities. To facilitate translation of results into practice for orphan drug evaluation, our communication will target academic, industrial research networks, the European Medicines agency (EMEA), and patient associations. The website administration will be handled by key staff members of WP7, while all team members will contribute to its content under the supervision of the project coordinator. This platform will consist in the project summary, major achievements and updated results, the content of presentations and meetings' minutes and useful links. Access to a public webpage of the project (including patient associations) will be made available both in scientific and in non-initiate language to disseminate knowledge to a wider community. Communication on the project will be made at local, regional, national and international levels. Results generated by the project will be submitted for publication in renowned international scientific journals in order to reach other experts in the field.

Industry partner: The modelling department of NOVARTIS (F. Bretz) will offer expertise in the field of RCT modelling and simulation, in collaboration with WP (1, 5 and 6).

8.3.4 Time plan including project management and reporting

Management plan. Partner one (UCBL) will coordinate the activities of the network and supervise the progress of all defined work packages. The objectives of the coordination are to initiate a goal-oriented scientific, administrative and financial management of the project; assure the quality of all project outputs and deliverables; organize regular technical, management, and other meetings; organize regular reviews in line with the instructions from the funding institution; make sure that

deliverables are produced in time, provide progress reports and deliverables within each project review period defined in the Grant Agreement.

The financial administrative and legal coordination will be supported by Lyon Ingénierie Projets, subsidiary of UCBL, which has gained experience in the administration of European projects. Every 12 months UCBL will prepare a consolidated overview of the budget on the basis of the financial statements received from the partners for submission to the funding Agency.

Responsibility for the Day-to-Day Management of the project is also in the hands of UCBL. A project mailing list will be set up to facilitate the exchange of documents and information. Periodic conference calls will be integrated, determined during the first quarter of the project.

To coordinate research, the network will set up and extensively use a communication infrastructure comprising a Web site. The web site structure will be set up and maintenance will be coordinated by WP7. The content of respective research themes will be provided by all teams (according to the teams' expertise). Each team focusing the research efforts on a particular area will link to further important information available, like the most relevant literature on this topic, or the sets of interesting problem instances.

A Network Supervisory Board (NSB) will be set up, with representatives of all partners chaired by UCBL as project coordinator. Responsibilities are divided as follows: Academic and Scientific.

Distribution of tasks and time plan:

WP	Role	Year 1		Year 2		Year 3	
WP 1	Coordination, methodology						
WP 2 to 4	Identification of diseases / models						
WP 5	Building the models						
WP 6	RCTs simulation						
WP 7	Results dissemination						

All WPs will be able to start working immediately after the kick-off meeting, and once contract and agreements have been finalized, and scientists have been recruited.

At the beginning of the project: first modelling strategies, identification of needs for each disease.

After 6 months: presentation of the results of bibliographic search after the first 6 months for existing models, available data, first model designs, with suggested improvements, establishing a hierarchical priority for modelling / simulating trials, according to availability of data.

After one year: presentation of preliminary results for one or more of the diseases, meeting for discussion and suggestion of improvements, definition of a strategy per disease. An agreement must be obtained between partners on the choice of the models to be used for RCTs simulation, the choice of the appropriate experimental designs to be tested in each clinical situation, and details on how to proceed to the next step.

Milestones: Contracts signed, Scientists recruitment, Presentation and approval of the final models for each clinical situation, strategy for simulation. Presentation / discussion on the first results of simulations, strategy for finalization, final results presentation and interpretation.

Deliverables: Kick-off meeting (month 2), Website and communication tools (month 6), Organization of scientific meetings (every 6 months), Periodic internal reports (every 6 months), Mid-term and final reports (month 18 and 36) and Platform of *in silico* simulation.

8.4 Complementarity of the teams and added value of international cooperation within the consortium and with other groups or organizations if applicable

CRESim is a multi-disciplinary project involving physicians, pharmacologists, mathematicians and computer scientists belonging to the academic or private sector. Academics have a long-standing experience of multi-disciplinary collaborative work within the modelling framework. Multi-disciplinary collaboration has become mainstream for individuals involved in modelling development. Collaboration with a private partner will give academics a better opportunity to see their research find an industrial application. All partners have in common the willingness to boost drug development in rare diseases affecting children. All know that finding a solution for a complex disease implies a transversal approach.

8.5 Potential economic and societal impact

Patients affected with rare diseases and their families are confronted with the lack of scientific knowledge (cf. difficulties in developing therapeutic tools and defining adequate therapeutic strategies). The cost of the few existing drugs is usually high and social consequences are major. CRESim project will contribute to speed-up the process of orphan drug development, and will transform our understanding of rare diseases and the practice of medicine in this domain.

8.6 Ethical and legal aspects

CRESim implies *in silico* use of available data from real patients databases, and no patient data collection; therefore it does not raise ethical issues. However, transfer of data across borders is an issue. All data transferred will be anonymous, with respect of the privacy of persons, and confidentiality. Regulatory requirements concerning data transfer will be fulfilled.

8.7 Plan for use and dissemination of knowledge

All the teams involved in the project are highly sensitive to the need to communicate obtained results to the scientific community and to the general public (including patient associations), as this topic is highly, timely relevant and applicable for future research in the field. Dissemination of results will be made swiftly through the usual channels of original papers submitted for publication to peer reviewed, international scientific journals, oral presentations and posters at conferences, workshops and seminars, as well as being described in regular (yearly) reports to the European Commission. In all cases, the financial support of the PRIOMEDCHILD Programme will be recognized in the appropriate section of the communication.

Specific web page. An important component of dissemination will be channeled through the public using a specific website with an informative forum both for healthcare professionals and for the public at large. The website will be established with a restricted and public area, respectively for internal issues and general information.

Education and training. Thanks to the wide range of complementary expertise assembled in this program, there will be ample opportunities for education and training in forefront fields of clinical pharmacology, pediatrics, biostatistics, and modelling, adding to the population of scientifically qualified personnel within the EU.

8.8 Scientific justification of requested budget

The largest proportion of the budget will be dedicated to hiring postdoctoral scientists and graduate students: one 3-year full time Equivalent (FTE) Scientist for WP1, scientific and technical co-ordination, one 3-year FTE for modelling, one 3-year FTE for simulation, one half time Equivalent for each condition to be studied (WP 2 to 4), one 3-year third time Equivalent for dissemination. Any funds for equipment are related to software licenses for modelling, statistical analysis, databases management and numerical simulation. The budget is completed by funding to cover the costs of attending scientific meetings both within the consortium as well as to International meetings/workshops; dissemination costs and any costs that may be incurred in exchanges in personnel between laboratories.

8.9 Handling of intellectual property rights within and outside the research consortium

Intellectual property. The partners will conclude a Consortium Agreement for the project, setting the rules for intellectual property, innovation-related activities and exploitation of results. Main rules are: i) pre-existing know-how: each contractor remains the sole owner of its intellectual and industrial property rights over its pre-existing know-how. The contractors agree that the access rights to the pre-existing know-how needed for carrying out their own work for the project shall be granted on a royalty-free basis, ii) ownership and protection of knowledge: knowledge will be the property of the contractor generating it. In case of joint invention, the contractors concerned will agree to maintain the relevant rights and set up the agreements in order to do so. Legal protection mechanisms should be investigated every time exploitable results have been achieved. Any Intellectual Property issue will be discussed within the Steering Committee meetings.

Ownership. Any invention or work will generally be owned by the partner who performed the relevant experiments taking into consideration any contribution of other partners of the consortium.

Exploitation. The outcome of the proposal will represent an important source of information of special interest to the pharmaceutical industry, whether private or public. Participants shall submit at the end of the project a technology implementation plan acceptable to the Commission, indicating all potential foreground rights and exploitation intentions.

8.10 References

- Bajard A, Chabaud S, Perol D, Boissel JP, Nony P. Revisiting the level of evidence in randomized controlled clinical trials: a simulation approach. Contemp Clin Trials. 2009 Sep;30(5):400-10.
- Blesius A, Chabaud S, Cucherat M, Mismetti P, Boissel JP, Nony P. Compliance-guided therapy : a new insight into the potential role of clinical pharmacologists. Clin Pharmacokinet. 2006;45(1):95-104.
- Boissel JP, Cucherat M, Nony P, Chabaud S, Gueyffier F, Wright JM, Lièvre M, Leizorovicz A. New insights on the relation between untreated and treated outcomes for a given therapy : effect model is not necessarily linear. J Clin Epidemiol. 2008 Mar;61(3):301-7.
- Boissel JP, Cucherat M, Nony P, Dronne MA, Kassai B, Chabaud S. New approaches in pharmacology: numerical modelling and simulation. Therapie. 2005 Jan-Feb;60(1):1-15.
- Chabaud S, Girard P, Nony P, Boissel JP; THERapeutic MOdeling and Simulation Group. Clinical trial simulation using therapeutic effect modeling: application to ivabradine efficacy in patients with angina pectoris. J Pharmacokinet Pharmacodyn. 2002 Aug;29(4):339-63.
- Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, Dulac O, Pons G. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet. 2000 Nov 11;356(9242):1638-42.
- Duffull SB, Chabaud S, Nony P, Laveille C, Girard P, Aarons L. A pharmacokinetic simulation model for ivabradine in healthy volunteers. Eur J Pharm Sci. 2000;10(4):285-94.
- Evans CH, Ilstad ST. Editors Committee on Strategies for Small-Number-Participant Clinical Research Trials. Small Clinical Trials : Issues and Challenges. Board on Health Sciences Policy. Institute Of Medicine National Academy Press. Washington, D.C. 2003
- Guerrini R, Pons G. (2000) Comparative study of the efficacy of stiripentol used in combination in severe myoclonic epilepsy in infancy (SMEI). A double-blind, multicenter, placebo-controlled phase III study. Universit`a di Pisa – IRCCS Tella Maris, Via dei Giacinti, 256018 Calambrone (PISA), Italy.
- Kassaï B, Chiron C, Augier S, Cucherat M, Rey E, Gueyffier F, Guerrini R, Vincent J, Dulac O, Pons G. Severe myoclonic epilepsy in infancy: A systematic review and a meta-analysis of individual patient data. Epilepsia, 49(2):343–348, 2008;
- Kimko HC, Duffull SB. Simulation for Designing Clinical Trials. A Pharmacokinetic-Pharmacodynamic Modeling Perspective. (Drugs and the Pharmaceutical Sciences, 2003, Vol 127). Edited by Stephen B. Duffull and Hui C. Kimko,
- Nony P, Boissel JP. Use of sensitivity functions to characterise and compare the forgiveness of drugs. Clin Pharmacokinet. 2002;41(5):371-80.
- Nony P, Cucherat M, Boissel JP. Revisiting the effect compartment through timing errors in drug administration. Trends Pharmacol Sci. 1998 Feb;19(2):49-54.
- Senn S. Cross-over trials in clinical research. First Edition: Wiley, Chichester, 1993. ISBN 0-471-93493-3
- Tiddens HA, Brody AS. Monitoring cystic fibrosis lung disease in clinical trials: is it time for a change? Proc Am Thorac Soc. 2007 Aug 1;4(4):297-8.
- Tiddens HA, de Jong PA. Imaging and clinical trials in cystic fibrosis. Proc Am Thorac Soc. 2007 Aug 1;4(4):343-6.
- Uyttebroeck A, Suciu S, Laureys G, Robert A, Pacquement H, Ferster A, Marguerite G, Mazingue F, Renard M, Lutz P, Rialland X, Mechinaud F, Cavé H, Baila L, Bertrand Y; Children's Leukaemia Group (CLG) of the European Organisation for Research and Treatment of Cancer (EORTC). Treatment of childhood T-cell lymphoblastic lymphoma according to the strategy for acute lymphoblastic leukaemia, without radiotherapy: long term results of the EORTC CLG 58881 trial. Eur J Cancer. 2008 Apr;44(6):840-6.
- Wang H, Boissel JP, Nony P. Revisiting the relationship between baseline risk and risk under treatment. Emerg Themes Epidemiol. 2009 Feb 17;6:1.

9. Brief CVs of each Research Partner representative

Dr. Patrice NONY (MD, PhD)

Date of birth: March 18, 1959; **Place of birth:** Lyon, France; **Languages:** French, English, German

Current Position: Permanent Hospital M.D., (Department of Clinical Pharmacology, University Hospital of Lyon, France); Titular member of the French National Authority for Health (commission de la Transparence)

Medical and scientific training

Medical residency (1982 - 1986), Doctor in Medicine, medical specialty: cardiology (1985)

Master in Pharmacology (1981), PhD in Clinical Pharmacology : 1998

Head of the Phase 1 unit: department of Clinical Pharmacology, Lyon (1989-2001)

Member of the French Society of Cardiology

Member of the French Society of Pharmacology and Therapeutics

Research activities

Participation to 21 phase I and 10 phase III clinical trials

Author/co-author of 9 academic funded research projects (including 1 for the EU Biomed 2 Program)

Author/co-author of 56 articles referenced in the US National Library of Medicine

Participation to scientific evaluation of projects for EU (2001, 2002):

- IST Program Information Society Directorate-General, Systems and Services for the Citizen, Applications relating to Health Unit
- Quality of life and management of living resources, area 7 (chronic and degenerative diseases, cancer, diabetes, cardiovascular diseases and rare diseases)

Five selected publications related to the CRESim project

1. Bajard A, Chabaud S, Perol D, Boissel JP, Nony P. Revisiting the level of evidence in randomized controlled clinical trials: a simulation approach. Contemp Clin Trials. 2009 Sep;30(5):400-10.
2. Blesius A, Chabaud S, Cucherat M, Mismetti P, Boissel JP, Nony P. Compliance-guided therapy: a new insight into the potential role of clinical pharmacologists. Clin Pharmacokinet. 2006;45(1):95-104.
3. Chabaud S, Girard P, Nony P, Boissel JP; THERapeutic MOdeling and Simulation Group. Clinical trial simulation using therapeutic effect modeling: application to ivabradine efficacy in patients with angina pectoris. J Pharmacokinet Pharmacodyn. 2002 Aug;29(4):339-63.
4. Duffull SB, Chabaud S, Nony P, Laveille C, Girard P, Aarons L. A pharmacokinetic simulation model for ivabradine in healthy volunteers. Eur J Pharm Sci. 2000;10(4):285-94.
5. Nony P, Cucherat M, Boissel JP. Revisiting the effect compartment through timing errors in drug administration. Trends Pharmacol Sci. 1998 Feb;19(2):49-54.

Prof. Yves BERTRAND
Born 06/05/58

Positions: Professeur des Universités-Praticien Hospitalier.
Head of the department „Hématologie-immunologie pédiatrique et de transplantation de moelle osseuse.(HCL)“ since 2004
Administrator of Institut d'Hématologie et d'Oncologie Pédiatrique (IHOP)

Titles: INTERNE DES HOPITAUX DE PARIS 1981
CES GENETIQUE HUMAINE GENERALE (NECKER) 1983
DEA DIFFERENCIATION , GENETIQUE ET IMMUNOLOGIE LYON 1995
DOCTORAT EN MEDECINE PARIS 1986
DOCTORAT D'UNIVERSITE LYON 2002

Address: Institut d'Hématologie et d'Oncologie pédiatrique
1 Place Joseph Renaut 69008 LYON
Tel 33 469166588 Fax 33 478782703 yves.bertrand@chu-lyon.fr

N° D'INSCRIPTION A L'ORDRE : 69/09279
N° ADELI 691092795

Recent publications

1/Domenech C, Mercier M, Plouvier E, Puraveau M, Bordigoni P, Michel G, BenoitY, Leverger G, Baruchel A, **Bertrand Y**. First isolated extramedullary relapse in children with B-cell precursor acute lymphoblastic leukaemia: results of the Cooprall-97 study. Eur J Cancer. 2008 Nov;44(16):2461-9.

2/**Bertrand Y**, Mechinaud F, Brethon B, Mialou V, Auvrignon A, Nelken B,
Notz-Carrère A, Plantaz D, Patte C, Urbieta M, Baruchel A, Leverger G.
SFCE (Société Française de Lutte contre les Cancers et Leucémies de l'Enfant et de l'Adolescent) Recommendations for the Management of Tumor Lysis Syndrome (TLS)With Rasburicase: An Observational Survey.
J Pediatr Hematol Oncol. 2008 Apr;30(4):267-271.

3/Uyttebroeck A, Suciu S, Laureys G, Robert A, Pacquement H, Ferster A,
Margueritte G, Mazingue F, Renard M, Lutz P, Rialland X, Mechinaud F, Cavé H,Baila L, **Bertrand Y**; on behalf of the Children's Leukaemia Group (CLG) of theEuropean Organisation for Research and Treatment of Cancer (EORTC).
Treatment of childhood T-cell lymphoblastic lymphoma according to the strategy for acute lymphoblastic leukaemia, without radiotherapy: Long term results of the EORTC CLG 58881 trial.
Eur J Cancer. 2008 Mar 12;

4/Crassard N, Hadden H, Pondarré C, Hadden R, Galambrun C, Piens MA, Pracros JP,Souillet G, Basset T, Berthier JC, Philippe N, **Bertrand Y**.
Invasive aspergillosis and allogeneic hematopoietic stem cell transplantation in children: a 15-year experience.
Transpl Infect Dis. 2008 Mar 4;

5/Baleydier F, Decouvelaere AV, Bergeron J, Gaulard P, Canioni D, **Bertrand Y**,Lepretre S, Petit B, Dombret H, Beldjord K, Molina T, Asnafi V, Macintyre E.T Cell Receptor Genotyping and HOXA/TLX1 Expression Define Three T Lymphoblastic Lymphoma Subsets which Might Affect Clinical Outcome.
Clin Cancer Res. 2008 Feb 1;14(3):692-700.

Prof. Renzo GUERRINI

Date of birth: 25/11/1956, **Place of birth:** Terni, Italy; **Nationality**: Italian; **Languages:** It, UK, Fr.
Current Position - Professor of Child Neurology and Psychiatry, University of Florence (Italy) and Head and Director, Pediatric Neurology Unit and Laboratories, University Hospital A. Meyer, Florence (since 2006); - Scientific Director – IRCCS Stella Maris, Pisa (since 2009)
Award: Ambassador for Epilepsy ILAE 2003

Member of the Editorial Board of the following peer reviewed journals/Book series:
• Journal of Child Neurology (1995-), • Epilepsies (1994-), • Epileptic Disorders (1998-), • Epilepsia (2000-2004)
• Seizure (Member of the CPD Committee 2001 - 2003 and Editorial board 2005-), • Neuropediatrics (2002-), • Neurological Sciences (2004-), • BMC Medical Genetics (2007-), • European Journal of Neurology (2009-) • Progress in Epileptic Disorders (Book Series) (2007-), • Topics in Epilepsy (Book Series) (2008-), **Associate Editor, Epilepsia (2006-2009; 2009-)**

Main research interests: His research group focuses on the clinical characteristics, neurophysiology, genetics and treatment of childhood epilepsies, on brain development and mental retardation. He has produced over 220 Articles on Peer reviewed journals: Impact Factor > 880; 10 books; H Index > 50. Invited speaker to more than 350 meetings worldwide. Has coordinated or participated to national and international research projects on Childhood Epilepsy, including the EU project EPICURE. His research activity is largely based on international collaborations with France, UK, USA, Japan and other countries.

Five selected publications:
1. Guerrini R, Dobyns WB, Barkovich AJ. *Abnormal development of the human cerebral cortex: genetics, functional consequences and treatment options*. Trends in Neurosciences 2008;31:154-62.
2. Guerrini R, Moro F, Kato M, Barkovich AJ, Shiihara T, McShane MA, Hurst J, Loi M, Tohyama J, Norci V, Hayasaka K, Kang UJ, Das S, Dobyns WB. *Expansion of the first PolyA tract of ARX causes infantile spasms and status dystonicus.* Neurology. 2007;69:427-33.
3. Guerrini R. *Epilepsy in children.* Lancet. 2006;367:499-524.
4. Sheen VL, Ganesh VS, Topcu M, Sebire G, Bodell A, Hill RS, Grant PE, Shugart YY, Imitola J, Khoury SJ, Guerrini R, Walsh CA. *Mutations in ARFGEF2 implicate vesicle trafficking in neural progenitor proliferation and migration in the human cerebral cortex.* Nature Genetics 36:69-76, 2004.
5. Porciatti V, Bonanni P, Fiorentini A, Guerrini R. *Lack of cortical contrast gain control in human photosensitive epilepsy.* Nature Neuroscience 3:259-263, 2000

Main Research projects (last 5 years only)
• ***Italian Ministry of Health***, Research Project 1/04: Degenerative myoclonic encephalopathies: molecular diagnosis, treatment and genotype phenotype correlations. (Coordinator: Period: 2005-07).
• ***Telethon Foundation*** GGP05177: Array-CGH election technique to study cerebral cortex malformations and epilepsy. (Unit Coordinator: 2005-2009).
• ***European Community EU***, Contract L SH-037315: Functional Genomics and Neurobiology of Epilepsy: a basis for new therapeutic strategies EPICURE (Subproject Coordinator; Period: 2007-11)
• ***Italian Ministry for University and Research*** (MIUR) Grant n°. 2006061871_002: Genetic bases and clinical characteristics of sleep related childhood epilepsies (Unit Coordinator; Period: 2007-09)
• ***Italian Ministry of Health*** Project. PS NEURO ex 56/05/13: Trinucleotide (GCG) repeat expansions of the ARX gene and progressive dystonia in infancy. Grant (Coordinator; Period: 2007-2009)
• ***Italian Ministry of Health*** (Istituto Superiore di Sanità). Project 526d/22: Usefulness of MLPA in the molecular diagnosis of lissencephalies and neuronal migration disorders (Coordinator; Period: 2007-10)
• ***Mariani Foundation.*** Grant R-08-72: Is epileptic encephalophathy a general diagnostic category? Assessing neuropsychology and behavior in children with severe Myoclonic Epilepsy of Infancy (Dravet syndrome) can demonstrate whether intractable seizures produce progressive disturbance in cerebral function in this disorder (Coordinator; Period: 2008-2009)

Prof. Harm A.W.M. TIDDENS
Prof. Dr. Harm A.W.M. Tiddens, born 1 December 1956 in Helmond.

EDUCATION

1985	Medical training, University of Amsterdam
1991	Specialist training pediatrics, Wilhelmina Children's Hospital Utrecht
1994	Training Pediatric Respiratory Medicine, Department of Pediatric Respiratory Medicine, Sophia Children's Hospital, Rotterdam (head: Professor JC de Jongste)
1998	Ph.D. thesis "Structure and function of chronically inflamed human airways". Promotor: Professor J.C. de Jongste, Erasmus University Rotterdam.

CURRENT POSITION

1994 - 2009	Pediatric pulmonologist, Dept. of Pediatrics, Subdivision Pediatric Respiratory Medicine (head: Professor JC de Jongste), Sophia Children's Hospital, Rotterdam.
1997 - present	Chairman CF-team Erasmus Medical Center. CF center is one of the 18 ECFS-clinical trial network centers
2006 - 2011	Visiting professor University of Washington School of Medicine (UWSOM), Children's Hospital & Regional Medical Center, Pediatric Pulmonary Division at the CF Therapeutics Development Network Coordinating Center (Prof. B. Ramsey) Seattle, USA. Sponsor CFF. Theme: Development of end-points
2007 - present	Honorary member dept. of Radiology, Erasmus Medical Center
2009 - present	Professor of Paediatric Respiratory Medicine, dedicated to the development of the lung

Selection of BOARDS AND COMMITTEES

1999 – present	Member of Erasmus MC/Sophia research committee
2005 – present	Editorial board member of Journal of Aerosol Medicine and Pediatric Pulmonology
2006 - present	Member of Eurocare CF group
2006 - present	Chairman of ERS- task force on CT in CF
2006 - present	Member editorial board Pediatric Pulmonology
2007 - present	Scientific committee European Cystic Fibrosis Conference, 2007
2007 - present	Member of elections committee of the European CF Society (ECFS)
2007 - present	Member of executive committee of the ECFS Clinical Trial Network (ECFS-CTN)
2008 - present	Deputy chair of the executive committee of the ECFS-CTN
2008 - 2009	Chair of the protocol review committee of the ECFS-CTN
2008 - present	Liaison between ECFS-CTN and the Cystic Fibrosis Foundation (CFF) therapeutic drug network (TDN)
2008 – present	Member of 'klankbordgroep' for Dutch representatives Paediatric Committee
2008 - present	Member of the Netherlands CF society-CTN
2008 - present	Member of the Medicines for Children Research Network for CF

5 selected publications

1. **Tiddens HAWM, de Jong PA**. Imaging and clinical trials in cystic fibrosis. *Proc Am Thorac Soc* 2007; 4: 343-346.
2. Gustafsson PM, De Jong PA, **Tiddens HA**, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. *Thorax* 2008; 63:129-134.
3. Loeve M, van Hal PT, Robinson P, de Jong PA, Lequin MH, Hop WC, Williams TJ, Nossent G, **Tiddens H**. The spectrum of structural abnormalities on CT scans from CF patients with severe advanced lung disease. *Thorax* 2009 Jun 18 [Epub ahead of print].
4. Loeve M, Lequin MH, de Bruijne M, Hartmann IJ, Gerbrands K, van Straten M, Hop WC, **Tiddens HA**. Cystic fibrosis: are volumetric ultra-low-dose expiratory CT scans sufficient for monitoring related lung disease? *Radiology* 2009 Aug 25 [Epub ahead of print].
5. **Tiddens HAWM**, Donaldson SH, Rosenfeld M, Pare PD. Cystic fibrosis lung disease starts in the small airways: Can we more effectively treat it? *Pediatr Pulmonol* 2010; 45:107-117

Prof. Leon AARONS
LEON JOHN AARONS

Date of birth: 19 MARCH 1948

EDUCATIONAL CAREER:

1964-68 B.Sc. (Physical Chemistry)
University of Sydney
1969-71 M.Sc. University of Calgary
1971-73 Ph.D. Theoretical Chemistry Department
University of Manchester
1973-75 I.C.I.Postdoctoral Fellow
School of Chemistry, University of Leeds

Academic career:
School of Pharmacy and
Pharmaceutical Sciences

1976-1991	Lecturer
1991-2002	Senior Lecturer
2002-2005	Reader
2005-present	Professor and Director of Undergraduate Studies

Current Address

School of Pharmacy and Pharmaceutical Sciences
The University of Manchester
Manchester, M13 9PT, U.K.
Tel: +44 (0)161 275 2357
email: leon.aarons@manchester.ac.uk

Recent publications

1. G. Langdon, I. Gueorguieva, L. Aarons, M. Karlsson. 'Linking preclinical and clinical whole-body physiologically based pharmacokinetic models with prior distributions in NONMEM', Eur.J.Clin.Pharmacol. 63, 485-498 (2007).
2. L. Dickinson, M. Boffito, S.H. Khoo, M. Schutz, L. Aarons, A.L. Pozniak, D.J. Back. 'Pharmacokinetic analysis to assess forgiveness of boosted saquinavir regimens for missed or late dosing', J.Antimicrob.Chemother. 62, 161–167 (2008).
3. M. Chenel, F. Bouzom, L. Aarons, K. Ogungbenro. 'Drug–drug interaction predictions with PBPK models and optimal multiresponse sampling time designs: application to midazolam and a phase I compound. Part 1: comparison of uniresponse and multiresponse designs using PopDes', J Pharmacokin.Pharmacodyn. 35, 635–659 (2008).
4. K. Ogungbenro, A. Dokoumetzidis, L. Aarons, 'Application of optimal design methodologies in clinical pharmacology experiments', Pharmaceut.Stat. 8, 239-252 (2009).
5. K. Ogungbenro, I. Matthews, M. Looby, G. Kaiser, G. Graham, L. Aarons, 'Population pharmacokinetics and optimal design of paediatric studies for famciclovir', Br.J.Clin.Pharmacol. 68, 546–560 (2009).

Research Interests

My major research interests lie in the area of pharmacokinetics. Although having a general interest in the subject as a whole I have a special interest in modelling and data analysis. I collaborate with members of the pharmacokinetic group in Manchester but also with other scientists in industry and academia throughout Europe. I have built a world-wide reputation in the area of population pharmacokinetics, which is evidenced by many invitations to talk at international meetings and within pharmaceutical companies (53 invited lectures at scientific meetings and 39 within either the pharmaceutical industry or university departments). Population pharmacokinetics is an increasingly important aspect of drug development within the pharmaceutical industry and is a discipline which is increasingly being utilised in specialised populations, and I have developed strong links with groups in Oxford and Liverpool involved in anti-malarial therapy.

Ms. Sylvie CHABAUD

Birth date and place: October 30, 1968 at Chagny, France
NATIONALITY: French
PROFESSIONAL ADDRESS:
Unité de Biostatistique et d'Evaluation des Thérapeutiques - Centre Léon Bérard - 28 rue Laënnec - 69373 LYON - CEDEX 08 - Email address: chabauds@lyon.fnclcc.fr

POSTGRADUATE EDUCATION AND TRAINING:
1990: DUT Statistique et traitement informatique des données, Grenoble (Two years university degree).
1996: DEST Informatique d'entreprise, CNAM Lyon (Four years university degree).
1998: DEA Analyse et modélisation des systèmes biologiques, Université Lyon I (Master degree in science).

PROFESSIONAL EXPERIENCE:
· **Previous appointment**
From 1990 to 2005
Biostatistician at APRET/EZUS – EA3637 – Pharmacology Clinic Unit,
Faculté LAENNEC,
Lyon - FRANCE
In charge of statistical analysis of phase I to III multicentric clinical trials (statistical considerations in protocol, statistical analysis plan, statistical report, publication); Statistical support of Data Safety Monitoring board; Teaching and training of students (statistics courses and training for the university certificate of investigators training for clinical trials and master 'Approches Mathématiques et Informatique du Vivant'); Modelisation pharmacokinetic and pharmacodynamic; Responsible of computer system of statistical department.
· **Present appointment**
Since 2005
Biostatistician at Centre Léon Bérard; Responsible of statistical team,
Lyon - FRANCE
In charge of statistical analysis of phase I to III multicentric clinical trials in oncology (statistical considerations in protocol, statistical analysis plan, statistical report, publication); Statistical support of Data Safety Monitoring board; Teaching and training of students (statistics courses and training for the university certificate of investigators training for clinical trials, master 'Sciences des Systèmes de Santé' and DUT 'Statistiques et Traitement Informatique des Données'); Consulting for researchers and practitioners; Managing and planning of statistic department.

STATISTICAL SOFTWARE: SAS, Nquery Advisor, Splus, R, NONMEM

PUBLICATIONS:
1. Bajard A, Chabaud S, Pérol D, Boissel JP, Nony P. Revisiting the level of evidence in randomized controlled clinical trials: A simulation approach. Contemp. Clin Trials. 2009 Sep;30(5):400-10.
2. Boissel JP, Cucherat M, Nony P, Dronne MA, Kassai B, Chabaud S. [New approaches in pharmacology: numerical modelling and simulation] Therapie. 2005 Jan-Feb;60(1):1-15.
3. Chabaud S, Girard P, Nony P, Boissel JP; HERapeutic MOdeling and Simulation Group. Clinical trial simulation using therapeutic effect modeling: application to ivabradine efficacy in patients with angina pectoris. J Pharmacokinet Pharmacodyn. 2002 Aug;29(4):339-63.
4. Duval V, Chabaud S, Girard P, Cucherat M, Hommel M, Boissel JP. Physiologically based model of acute ischemic stroke. J Cereb Blood Flow Metab. 2002 Aug;22(8):1010-8.
5. Laporte-Simitsidis S, Girard P, Mismetti P, Chabaud S, Decousus H, Boissel JP. Inter-study variability in population pharmacokinetic meta-analysis: when and how to estimate it? J Pharm Sci. 2000 Feb;89(2):155-67. Review.

PONS Gérard, Julien, Léopold, Born 30 November 1947 in Paris 18th,

INSTITUTION AND LOCATION
Service de Pharmacologie Clinique, Hôpital Saint-Vincent de Paul, Université René Descartes, , 82, avenue Denfert-Rochereau
75674 PARIS CEDEX 14 (FRANCE)

CLINICAL PHARMACOLOGIST - PEDIATRICIAN

TITLES AND APPOINTMENTS

. *December 1996-present*
Head of the Department of Perinatal and Pediatric Pharmacology
Hôpital Saint-Vincent de Paul - Paris

. *November 1991-present*
Professor of Clinical Pharmacology - Hospital Physician
[Professeur des Universités - Praticien Hospitalier (J.O. du 16 juillet 1991)]
Pharmacologie Périnatale et Pédiatrique, Hôpital Saint-Vincent de Paul
Faculté de Médecine Cochin-Port Royal - Université René Descartes (Paris V)

TRAINING

. *November 1987 - November 1991*
Associate Professor of Clinical Pharmacology - Hospital Physician
(Maître de conférence des Universités - Praticien Hospitalier)
Pharmacologie Périnatale et Pédiatrique, Hôpital Saint-Vincent de Paul
Faculté de Médecine Cochin-Port Royal - Université René Descartes (Paris V)

. *November 1984 - November 1987*
Assistant Professor of Clinical Pharmacology - Hospital Physician
(Assistant des Hôpitaux de Paris - Assistant de l'Université René Descartes)
Pharmacologie Périnatale et Pédiatrique, Hôpital Saint-Vincent de Paul
Faculté de Médecine Cochin-Port Royal - Université René Descartes (Paris V)

. *November 1981 - November 1984*
Assistant Professor of Pediatrics - Attending Physician
[Chef de Clinique de l'Université René Descartes - Assistant des Hôpitaux de Paris (Pediatrics)]
Service de Pédiatrie B (Head : Professor Jean Badoual)
Hôpital Saint-Vincent de Paul - Faculté de Médecine Cochin-Port Royal

. *November 1979 - November 1981*
Post-Doctoral Research Fellow
Division of Clinical Pharmacology-Departments of Pediatrics and Pharmacology - University of Minnesota - Minneapolis (USA)

. *November 1975 - November 1979*
Pediatric Resident (Interne des Hôpitaux de Paris)

5 selected publications

1. Bouillon-Pichault M, Jullien V, Piketty C, Viard JP, Morini JP, Chhun S, Krivine A, Salmon D, Dupin N, Weiss L, Lortholary O, Pons G, Launay O, Treluyer JM. A population analysis of weight-related differences in lopinavir pharmacokinetics and possible consequences for protease inhibitor-naive and -experienced patients. Antivir Ther. 2009;14(7):923-9.
2. Manolis E, Pons G. Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol. 2009 Oct;68(4):493-501.
3. Bouillon-Pichault M, Jullien V, Azria E, Pannier E, Firtion G, Krivine A, Compagnucci A, Taulera O, Finkielsztejn L, Chhun S, Pons G, Launay O, Treluyer JM. Population analysis of the pregnancy-related modifications in lopinavir pharmacokinetics and their possible consequences for dose adjustment. J Antimicrob Chemother. 2009 Jun;63(6):1223-32. Epub 2009 Apr 22.
4. Chhun S, Jullien V, Rey E, Dulac O, Chiron C, Pons G. Population pharmacokinetics of levetiracetam and dosing recommendation in children with epilepsy. Epilepsia. 2009 May;50(5):1150-7. Epub 2009 Jan 19.
5. Facilitation of drug evaluation in children by population methods and modelling. Tod M, Jullien V, Pons G. Clin Pharmacokinet. 2008;47(4):231-43. Review.

Dr. Frank BRETZ

Education

1996 M.Sc. in Mathematics at the University of Erlangen-Nürnberg, Germany
1999 Ph.D. in Statistics at the University of Hannover, Germany
2004 Post-doctoral thesis ("Habilitation") at the Hannover Medical School

Current Position: Global Head of the Statistical Methodology group at Novartis Pharma AG - Adjunct Professor at the Hannover Medical School, Germany

Other Positions

04/99 – 03/00 Statistician at Byk Gulden Pharmaceuticals, Konstanz
04/00 – 09/04 Assistant Professor at the Lehrgebiet Bioinformatik, University of Hannover
08/00 – 09/00 Research visit at Texas Tech University, USA
08/01 – 09/01 Research visit at Ohio State University, USA
07/02 – 11/02 Research visit at University of California Berkeley, USA
since 10/04 Member of the Statistical Methodology group at Novartis Pharma AG with increasing responsibilities; 11/08 – 04/09: US Head

Awards

2001 Young Researcher Award of the European Community at the "Inaugural Euro Conference of the Eastern Mediterranean Region of the International Biometric Society", Athens, 2001
2008 Editor's favorite paper for 2007 (*Pharmaceutical Statistics*; Senn and Bretz, pp. 161), presented in the Editor's Choice Sessions at the Annual PSI/EFSPI conference in Brussels and the XXIVth International Biometric Conference in Dublin, both in 2008
2008 Novartis Leading Scientist award for the scientific contributions to the company
2009 New Horizon Award for the continuous work on advanced dose-finding designs at Novartis
2009 Best Presentation of a Biopharmaceutical Contributed Paper for the JSM
2008 presentation on "Response-Adaptive Dose Finding Combing Multiple Comparison and Modeling Approaches"; presented at the JSM 2009 Biopharmaceutical Section meeting in Washington, D.C.
2009 Honorable mention in the Innovation category of the 2009 Pharma CEO Awards for "ground-breaking work in developing and implementing new design and analysis methods for defining optimal dosing".

5 selected Publications

1. Bretz, F., Dette, H., and Pinheiro, J. (2010) Practical considerations for optimal designs in clinical dose finding studies. *Statistics in Medicine* 29, in press.
2. Glimm, E., Maurer, W., and Bretz, F. (2010) Hierarchical testing of multiple endpoints in group-sequential trials. *Statistics in Medicine* 29(1), in press.
3. Brannath, W., Bretz, F., Maurer, W., and Sarkar, S. (2010) Trimmed weighted Simes' test for two one-sided hypotheses with arbitrarily correlated test statistics. *Biometrical Journal* 52, in press.
4. Latif, M., Bretz, F., Brunner, E. (2009) Robustness considerations in selecting efficient two–color microarray designs. *Bioinformatics* 25(18), 2355-2361.
5. Liu, W., Bretz, F., Hayter, A.J., and Wynn, H.P. (2009) Assessing non-superiority, non-inferiority or equivalence when comparing two regression models over a restricted covariate region. *Biometrics* 65(4), 1279-1287.