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AN INTERVIEW WITH SIMBEC- ORION ON THE CHALLENGES AND TRENDS OF RARE DISEASE CLINICAL TRIALS AT THE WORLD ORPHAN DRUGS CONGRESS USA, WASHINGTON, APRIL 2017

Simbec-Orion is an international full-service clinical research organisation, inspired to deliver outstanding solutions to the most challenging clinical research and development projects across the biotechnology and pharmaceutical space.

FABRICE CHARTIER

GROUP CHIEF OPERATING OFFICER, ORION CLINICAL SERVICES

Fabrice was appointed COO of Simbec-Orion upon completion of the merger of Simbec Research and Orion Clinical Services in June 2014. In 1998, Fabrice and Dr Alan Irvine founded Orion Clinical Services Ltd, an international CRO operating and specialising in Rare and Orphan diseases, oncology and other indications with high medical need.

In 1994, Fabrice founded Fournier Laboratories, a medium-size French pharmaceutical company, specialising in Gene Therapy and Immunotherapy. Previously, he was one of the directors of an international CRO based in Paris.

Dr CARLOS CAMOZZI

GROUP CHIEF MEDICAL OFFICER, ORION CLINICAL SERVICES

Carlos joined Orion Clinical Services two years ago, and has world-wide responsibility for the Clinical Research, Development and Pharmacovigilance activities of the Simbec-Orion (Slough, United Kingdom).

A Physician by training, with specialisations in Pediatrics, Clinical Pharmacology and Neuropsychiatry; Carlos has extensive experience in review, design or execution of more than 20 oncology, 31 pediatric and 52 orphan clinical trials from phase I to phase III.

He successfully led several regulatory interactions/consultations, orphan drug designations, pediatric investigational plans and marketing authorisations with the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA).

Other outstanding achievements - among others - is the approval of Carbaglu in NAGS deficiency by the FDA and the first ever approval (EMA) of a Gene Therapy (Glybera) in the western world.

Carlos has also actively participated in financial activities, due diligences, fundraising and financial rounds, in collaboration with several worldwide VCs to review, analyse and define the investment attractiveness of the development strategies of innovative R&D companies.

INTRODUCTION

Despite the attractiveness of orphan drugs (ODs), cash burn minimisation is one of the major challenges faced.

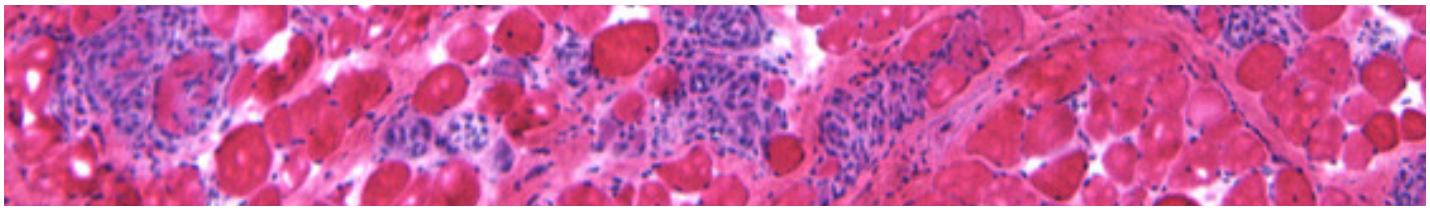
There may be some rules for the most efficient OD development but they should be adapted to challenges presented by each of the more than 7000 recognised rare diseases (RDs).

The clinical development of orphan drugs represents a very interesting challenge that demands thoughtful and innovative designs.

OD clinical developers must become serious, reliable players in the orphan space to attract investors and motivate all the stakeholders. The regulatory process of ODs is becoming more transparent and faster in the review step. Commercial success is not a guarantee and the regulatory and access demands are rising.

As a consequence, OD developers are focusing their interest in the "ultra-rare" diseases field which is characterised by conditions that are chronic or degenerative and by poor quality of life and/or shortened lifespans.

Given the increasing scrutiny of market access for ODs, it is crucial high-quality clinical data, clinically-meaningful endpoints rather than surrogate endpoints, life expectancy/survival, health economics evaluations and proper labelled indication are part of clinical trials with ODs.



Historically ODs have been rewarded with very high prices, however the current annual price per patient, faces tougher demands. This is despite the median current cost per patient being 5.5 times higher for ODs compared to non-ODs.

The main objective of research and development of orphan drugs is to bring a safe and effective treatment to the patients in the shortest period of time while protecting the investment by increasing certainty and prioritising the quality of data through innovative procedures.

There are many regulatory benefits related to the orphan drug designation in order to bring a safe and effective therapeutic option to patients who are often children, suffering from rare diseases.

Three main factors will affect the final cost of the proposed entire clinical development programme: time, quality and scope of work.

The purpose of clinical development is to bring into the market innovative treatments to overcome the unmet medical need. Therefore, the clinical trial design should enable the generation of the highest quality data to facilitate the regulatory review and approval, as well as answer market access requirements.

The efforts allocated to cope with the development scope must be maximised, considering the efforts per "rare disease" patient may be much higher than more conventional conditions. The completeness of the non-clinical experience and the adequate product development/production campaign are relevant factors at the time of launching the clinical development programme.

KEY CHALLENGES TO IMPROVE COST-EFFICIENCY IN ORPHAN DRUGS CLINICAL DEVELOPMENT

The key challenges in orphan drug development are inherent to the rarity of the disease, the scientific and medical knowledge and the timely accurate diagnosis. They can significantly limit the "feasible sample size" and as a consequence, make patient identification extremely difficult regarding potential recruitment and retention issues. Opening multiple centres does not necessarily lead to an effective recruitment process; however, it will certainly increase the cost of the study and the number of inactive/dormant sites.

There are many ways to improve the efficiency of recruitment working together. This can include collaboration with patient advocacy groups to implement an extensive awareness campaign related to the disease and to the proposed clinical development programme, targeting patients and their relatives but also physicians and nurses. Social media platforms (Twitter, Facebook, Snapchat etc and emerging digital tools such as wearable-devices and study-specific apps for mobile phones and tablets) offer a wide variety of important two-way communication tools with these audiences.

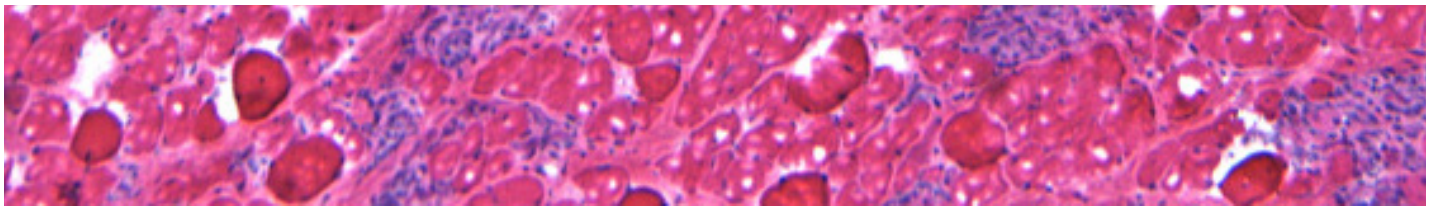
Other methods include the organisation of webinars involving scientific and medical experts, the publication of research experiences, the participation and support of disease registries, the attendee in focused conferences/congresses, the set-up of a dedicated study specific websites to keep all stakeholders informed about diagnosis tools, progress of the interactions with the regulatory agencies, names of the reference sites, interactive Q&A section, allocating the possibility to communicate via email to address questions related to the disease and the proposed clinical development programme.

The involvement of reference centres in clinical trials requires the full understanding of patient management - wherever they are - and the coordination of bringing those patients to the investigational sites.

The design of the clinical trial should be aligned to the regulatory expectations upon the proper interaction with the regulatory agencies.

The clinical study endpoints should bring the accurate answers and strongly support the clinical benefit via the appropriate translation of the preclinical data, the development of relevant clinical and biological markers, the modelling and simulation of the dose (especially when the target population are different paediatric groups) and the implementation of innovative and adaptive designs.

Clinical trial data recording and management must be assured regarding their quality and completeness to allow a robust statistical analysis - despite the small sample size. The ongoing data review and database soft locks will mitigate any delay in the data management process and bring higher confidence at the time of the final data-base lock.



REGULATORY EVOLUTION IN THE REVIEW PROCESS OF ORPHAN DRUGS

The regulatory requirements for the development of orphan drugs are continuously evolving in order to bring more transparency to regulatory expectations, to review the documentation and hopefully approve the application.

Various guidelines have been created to provide drug developers with a platform to build-up the specific clinical development plan. Several pathways are available to request interaction, consultation and advice to agree on the right clinical development design. The data generated during the non-clinical experiences should bring reasonable safety confidence to enter into humans.

Non-clinical experiences should bring information to anticipate the drug impact on metabolic pathways (e.g. CYP, transporters, etc) and the potential of DDI. Preclinical experience should select the appropriate animal species and age to support dose modelling and simulation.

Pre-clinical efforts should explore relevant markers to evaluate response to treatment and develop/validate the assays to be used in clinical trials. Regulatory agencies create consistent guidelines to cover the reality of rare diseases like small sample size, different statistical models and paediatric patients.

New accelerated review and approval processes motivate drug developers to invest efforts and bring more certainty to select a clinical development and regulatory strategy.

FOLLOWING SAREPTA'S EXONDYS51 APPROVAL, HOW WILL THE EVALUATION OF CLINICAL BENEFITS CHANGE BASED ON ENDPOINTS?

Exondys51 approval is an example related to the very high unmet medical need in a devastating, progressive and life-threatening rare disease.

Science is rapidly progressing to identify all possible mutations to individual RDs.

Paramount efforts are applied to determine the correlation between the genotype and phenotype. This fact triggers the hypothesis that certain patients with the same disease but different mutation may respond differently to the proposed treatment.

The FDA approval of Exonys51 may be considered as controversial and motivated by the willingness to allow DMD patients access to potentially life-saving drugs while imposing significant post-approval efforts to the drug developer.

There were very few exceptional cases (e.g. Carbaglu) where the FDA approved an orphan drug based on limited or incomplete clinical trial data with the mandatory requirement to generate appropriate clinical data and long-term follow-up of all patients treated with that drug. Glybera, the first-ever approved gene therapy in the western world, is another exceptional example that took not months but years to access the European market.

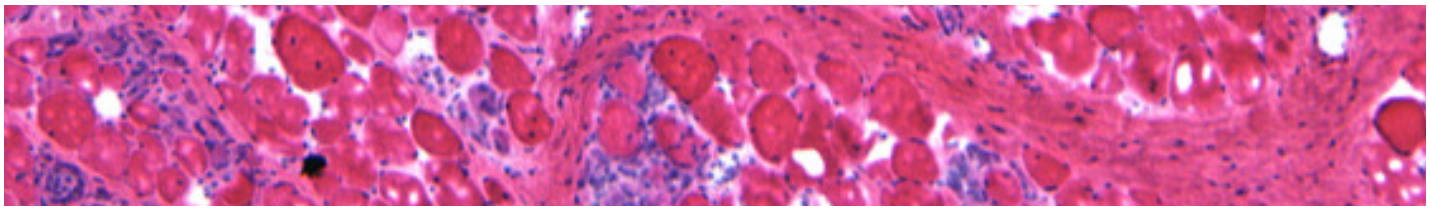
These approvals should not be considered as a new standard of regulatory review and approval process for ODs. The immediate impact of the exceptional approval of Exondys51 is represented by the initial discrepancies among US health insurers to cover this new treatment to cost/reimbursement.

As a conclusion, every orphan drug clinical development plan should be creative enough to design the endpoints that would facilitate the regulatory review and approval processes; as well as bring confidence of smooth, fast and successful market access.

WHAT ASPECTS OF COMMERCIALLY PLANNED CLINICAL TRIALS CAN BE IN CONFLICT TO MINIMIZING CASH-BURN DURING ORPHAN DRUG DEVELOPMENT? HOW DO YOU PLAN FOR SCALE UP WHILE IMPROVING COST-EFFICIENCY?

Most of the currently approved orphan drugs are disease-modifying treatments. Clinical trials are designed to generate robust data on safety and efficacy of the new therapeutic option. The impact on quality of life and other added benefits must be included in the clinical trial evaluation.

There are not many opportunities to perform commercially planned clinical trials with orphan drugs. It is necessary to differentiate the clinical development of orphan drugs in oncological rare diseases and non-oncological diseases.



In the oncological rare diseases - with the clinical development environment ever more competitive - the objectives of studies should integrate the new proposed treatment with existing standard of care and take into consideration that endpoints are more demanding and the existing treatment guidelines do - and will - influence the study design.

In these cases, the scale-up must be anticipated upon a well-defined decision tree model based on consistent and meaningful data obtained in research, pre-clinical and early clinical steps.

WHAT ROLE DOES MULTI-STAKEHOLDER COLLABORATION IN RARE DISEASE RESEARCH PLAY IN IMPROVING CLINICAL TRIALS COST-EFFICIENCY?

In ODs, it is essential to create a fully coordinated multidisciplinary research and development consortium involving academic researchers, clinical experts, patient associations, statisticians and drug developers. More than 65% of clinical programmes failed (H Ledford, Nature 477, 526-528, 2011) after completion of Phase II and III clinical studies, due to the lack of appropriate, reliable and validated research outcomes.

The information generated by academic research should be performed through an efficient working model to generate meaningful data to be analysed and translated into powerful clinical endpoints. The participation of interest groups such as patients, insurers and regulators will provide significant input on the expected benefits of the proposed new therapeutic option.

All the relevant markers, clinical and biological, must be validated from early steps and adapted to clinical application, in order to bring confidence on the safety and efficacy data-generated in research and clinical development. Every activity of the multi-stakeholder consortium should be aligned to the ultimate objective; to generate robust information that fully supports the clinical benefit of the OD in the specific indication.

Although there is no simple solution for preventing Phase II and III failures, several approaches can be developed to anticipate potential risks. A highly capable CRO may include the following recommendations:

- Applying more rigor and discipline to the development process avoiding shortcuts.
- Apply proper interpretation of the inputs of regulators and integrate them into the clinical trials.
- Adequate understanding of critical components in earlier development phases in order to reduce later-stage failures.
- Apply more disciplined protocol review and optimization, as well as use of modeling and simulation, adaptive trial designs, and biomarkers.
- Mitigate study execution risks: it should leverage data from a variety of sources and conduct ongoing surveillance of the quality of data being collected, while tying this to a properly planned risk-based monitoring protocol.
- Ensure completeness and clarity of submissions for regulatory agencies, seek advice from regulators during the drug development process in order to discuss the plan and identify areas of concern that may need adjustment.

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