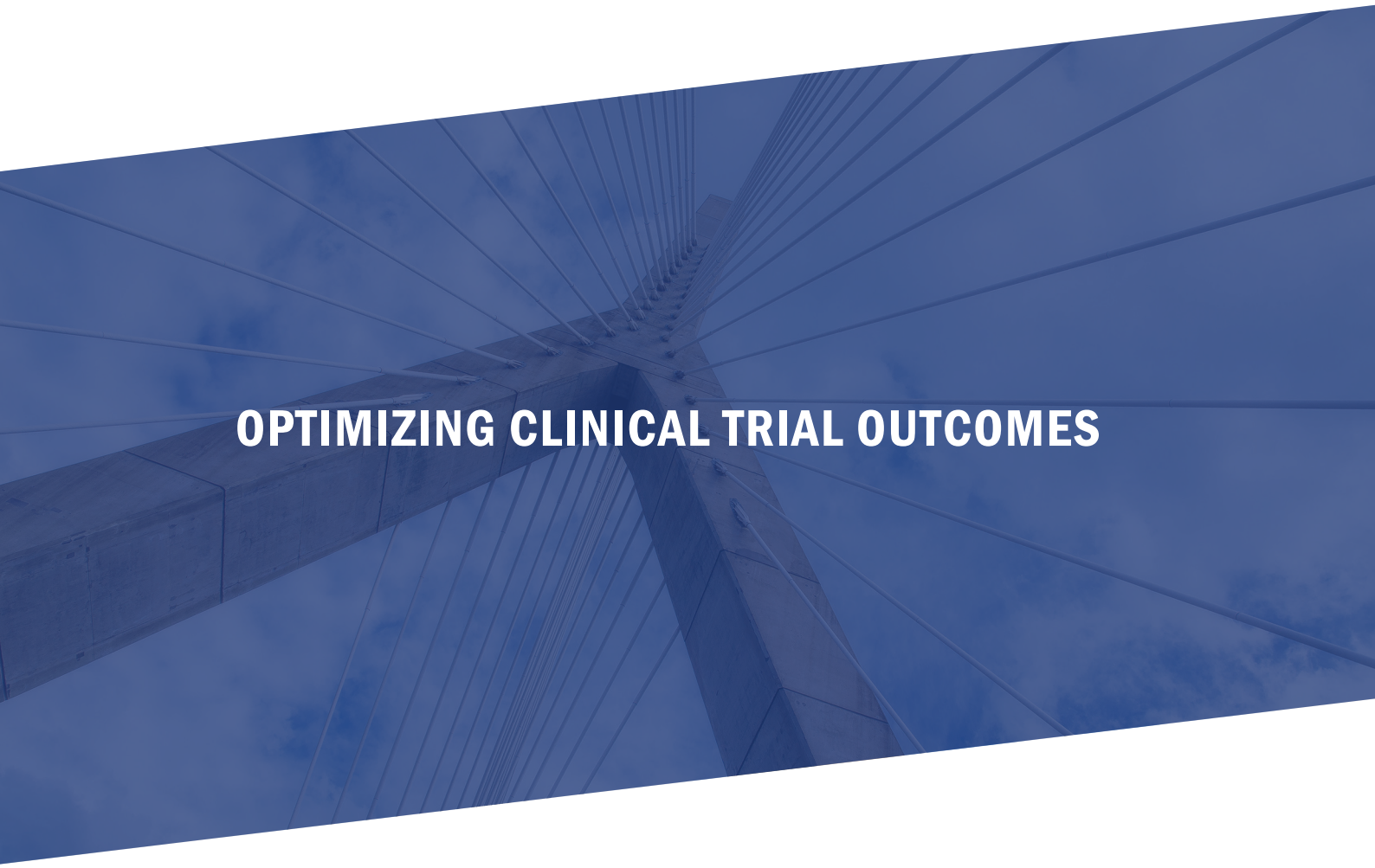
Boston Biotechnology Summit

Pre-SUMMIT INTERVIEW SERIES #4

3 CEO's Expert Opinion: On Biomarkers, Cardiac Safety, Modeling & Simulation.



OPTIMIZING CLINICAL TRIAL OUTCOMES

The 5th Boston Paris Biotechnology Virtual Summit

30 September 2021

Pre-SUMMIT
Interview Series #4

Modeling & Simulation

« Modeling & Simulation Strategies Must Be Integrated into Clinical Development As Early As Possible »

Bernard ORLANDINI, President and Co-founder of PhinC Development

Bernard Orlandini is President and co-founder of PhinC Development [Pharmacometrics & integrated Clinical development] based in the Greater Paris-Saclay Region and Evry Genopole Research and Biotechnology Hubs, France. He is an expert in early drug development and has more than 25 years of experience, having held many positions in the pharmaceutical industry as a biostatistician, project leader for early drug development and Director of Pharmacometrics. He also benefited considerably from being mentored by and working with pioneers in the field in France. He witnessed and was an actor in the morphing of Biometrics into Pharmacometrics, the advent of Population PK and PBPK and finally, the expansion of these techniques into Study Design and Clinical Development. He holds two Master's degrees; one in physiology and molecular biology and another in biostatistics, as well as a Postgraduate Diploma in clinical research and epidemiology.

Based on your expertise and experience, how can pharmacological modeling be optimized and positioned within an overall clinical development plan? What do you consider as best practice in this area? Are there any case studies you might like to share? And perhaps you could also tell us about the current views of regulatory agencies regarding modeling techniques?"

We all know the expression "There are no perfect models, only useful ones"! The integration of modeling in a program may very well start in the Lead Optimization sequence and then move along CMC with the assessment of cost-optimization in parallel on the drawing board. This early integration includes toxicological preclinical assessments and clinical pharmacology, and may then continue until phase III registration studies. The initial requests we used to receive at PhinC concerned gap analysis and trouble-shooting during clinical development. Sometimes, these gaps were revealed following meetings with regulatory bodies – and notably the FDA – when many previously unanswered questions were put on the table by the regulatory reviewers. The reputation of PhinC Development has also been greatly enhanced by our collaboration with Simulation Plus®, which develops absorption, distribution, metabolism, excretion, and toxicity modeling and simulation software for the pharmaceutical and biotechnology industries. Modeling techniques have improved considerably since 2015 following numerous publications and the emergence of artificial Intelligence deep learning. And since 2018, the requests we have received from Sponsors have evolved to include PK/PD modeling in the comprehensive clinical development plan. Currently, our collaborations include responding to gaps after assessments by the regulatory agencies (15%), standard modeling (15%), pharmacometrics in translational research (including First-In-Human) (~50%), and early and full integration in clinical development planning (20%).

Finally, one should not lose touch with the fact that modeling needs to be validated by experimentation, i.e. preclinical and clinical studies.

About PhinC Development

Founded in 2008, PhinC Development is an expert partner for small to medium-sized pharmaceutical or biotech companies who need to move forwards in early drug research. PhinC Development helps them to take the best decisions concerning drug development using all existing pharmacology and pharmacometrics modeling & simulation (M&S) tools. PhinC is structured around three pillars:

1) Biotechnological orientation with particular focus on Translational Science,
2) Pharmacometrics techniques,
3) Application of pharmacometrics to Drug Development.

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ACTIVE BIOMARKERS
Guiding your decisions

Biomarkers

« Biomarkers are not a trend, biomarkers are an obligation! »

Marc ESSODAIGUI, CEO of Active Biomarkers

Marc ESSODAIGUI is CEO of ACTIVE BIOMARKERS based in Lyons, France. He has more than 25 years of experience as a scientist and senior executive in the biotechnology industry. Before joining Active Biomarkers, Marc was the COO of ENDODIAG, a Paris-based biotech company developing non-invasive diagnostic solutions in endometriosis; VP Business Development at IPSOGEN (now Qiagen) in Marseilles and Director of Business Development at REED-ELSEVIER in Paris. Throughout his career, Marc has successfully developed and commercially launched products and services, managed global networks of distributors, and contributed to successful M&A and fundraising operations, including the IPSOGEN IPO. Marc ESSODAIGUI holds a PhD in Molecular Biophysics from the University of Paris 6 and the University of Caracas (Venezuela), and a Master's in Strategic Marketing.

How do you define/characterize an optimal Biomarker and then integrate the best Clinical Development strategy and operational plan?

A biomarker is a measurable indicator of a biological state or condition. An optimal biomarker needs to be:

Reliable, Simple to measure and Cost-effective. Active Biomarkers develops, validates and implements immuno-assays and cell-based assays in the context of clinical studies with particular focus on safety assessment, patient monitoring, diagnosis, prognosis, prediction, susceptibility or drug responses.
As a starting point, we study the pathophysiology of a disease in order to define relevant safety and efficacy biomarkers. Starting with recommendations, a Biomarker Panel is set up and ultimately transferred to that study Sponsor.

Over the past 10 years, Biomarker Driven Drug Development has become the new gold standard! As a case study for example, the recent and much discussed, approval of Aducanumab by the FDA demonstrated the importance of integrating an appropriate and robust biomarker strategy when developing new treatments. Biomarker identification starts during the early phases of target identification and validation. Once the biomarker has been identified, the Team needs to develop robust and reliable assays for its detection/quantification. The analytical performance of the resulting assay can then be confirmed in the context of non-interventional cohorts.

Finally, clinical studies are designed to enable full use of the biomarker to identify the correct patients and the right doses for a drug candidate, based on both safety and efficacy criteria. It is important to emphasize two points (a) the regulatory alignment of the biomarker, and (b) commercial considerations, with availability and reliability topping that list. Last but not least, cost-effectiveness needs to be assessed carefully in order to strike a balance between medical need and the constraints of the study budget.

About Active Biomarkers

What do all innovative therapies under development have in common? Whether in the preclinical or clinical stage, they all require robust and reliable biomarker assays, sound PK-PD methods and immunogenicity assessments. Active Biomarkers is an integrated laboratory which can offer decades of experience in the development, validation and implementation of analytical methods. Its know-how is acknowledged in four major therapeutic areas: oncology, infectious diseases, inflammatory pathologies, and neurodegenerative diseases. Active Biomarker's scientific/technical teams are members of several expert working groups who contribute to improving Good/Best Practices for the development and validation of bioanalytical methods used in the context of clinical trials. Beyond its state-of-the-art flow cytometry and ELISpot capabilities, Active Biomarkers can offer the broadest possible panel of immunoassay technologies, ranging from standard ELISA to multiplexed methods such as Luminex, Gyros or ELLA systems, and ultra-sensitive technologies such as MSD or Simoa.

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Cardiac Saefty

« Cardiac Safety is our DNA, now integrating multiple technologies »

Alexandre-Durand SALMON, CEO, BANOOK Group

Alexandre-Durand SALMON is CEO of the BANOOK Group based in NANCY, France. He is a corporate executive with broad leadership experience with start-up and emerging growth companies. Alexandre has a strong technical background in medical device industries and the clinical development of biopharmaceuticals and healthcare services. His past experience includes the scaling-up of a global clinical trials services company from start-up to raising capital to profitability. Alexandre Durand-Salmon co-founded KIKA Medical in 1997 (EDC Clinical Provider) and led it to its successful purchase by Merge Healthcare (now an IBM company). He has been with the Banook Group (cardiac safety, central imaging services provider) since 2010, and worked in various management positions before his appointment as CEO. His specialties are Creation, Innovation, Healthcare-related business applications, Internet, Medical Imaging, Clinical Trials, Medical Devices and Biosensors, all embraced with Passion.

How has your approach optimized the establishment of Cardiac Safety and ruling out the risk of an agent having cardiac toxicity? And could you explain the current criteria used to define optimal Cardiac Safety, and tell us how they are generally integrated and coordinated with the main "corpus' of an in-person or virtual clinical trial?

There are three pillars to our approach: (1) Alignment with the standardized E14 regulatory framework regarding the assessment of QT prolongation, which was revised in 2014. This updated version includes new modeling and product concentration-based assessments which enable robust conclusions without recourse to the QT Study. (2) Strategic support in order to provide the Sponsor with the right partner at the right time for cardiac safety assessments. Recommendations to the Sponsor are therefore the first step in integrating a clinical development process. (3) Innovation that includes "think out of the box" research on the relevant methodologies. To sum up, we ensure that our experienced team with expertise in technical subject matter will work in careful alignment with standard regulatory rules. In terms of clinical development, Cardiac Safety is in our DNA but over time we have on-boarded new and complementary tools such as Central Imaging and Quality of Life surveys in an attempt to offer a "One Stop Shop" and increase our efficiency. In clinical trials our focus is mainly cardiovascular through stringent evaluations based on ECG and Cardiac Ultrasound findings, all combined in an "Endpoint Adjudication" process. We therefore adopt a "transversal' approach based on key and core endpoints. In our experience, we may become involved in clinical studies at either an early (50%) or late (50%) phase. QUALITY is the key objective; this is driven by not only the quality of data but by robust IT that can secure the data, and we also offer reliable and trustworthy logistical support, comprehensive training programs and Q/C processes that are all put in place in a timely manner. I would like to emphasize the importance of the advent of virtual clinical trials which may involve equipping patients with wearable biosensors, for example, as well as many other patient-centered and patient-friendly technologies. The cost-effectiveness of virtual clinical trials can be seen from recent experience, where the shut-down of phase III studies due to external constraints could be avoided. To end on a positive note, we are encouraged by the high patient acceptability of these technologies, including in our senior patient population groups.

About Banook Group

Founded in 1999, Banook Group is one of the few established international providers capable of supplying Cardiac Safety, Central Imaging, Endpoint Adjudication and eCOA solution services. Through its qualitative, medical and regulatory expertise and innovative solutions, Banook Group has become a key player in clinical trials and benefits for patients worldwide.