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Groupe *de* Métabolisme *et* Pharmacocinétique

FIH workshop _ Final agenda

Chasing optimum First-In-Human (FIH) dose:

A key consideration to design Phase I clinical drug development

– Case studies for synthetics and biologics modalities -

31.05.2024

Espace Diderot, Paris 12^{ieme}

FIH Workshop
Agenda

Chasing optimum First-In-Human (FIH) dose:
A key consideration to design Phase I clinical drug development
– Case studies for synthetics and biologics modalities -

9h – 9h30
Welcome coffee

9h30 – 10h
Introduction

Set up the scene on FIH dose selection: Regulatory environment and beyond
Virginie Boulifard, Ipsen

10h – 12h
Synthetic molecules

Physiologically Based PharmacoKinetics (PBPK) for 1st in Human studies
François Bouzom, Simulation Plus

12h – 13h30
Lunch « Le Paris Lyon »

13h30 – 14h30
Biologics

Strategies for dose selection of biotherapeutics in First-in-Human studies
Antoine Deslandes, Sanofi

14h30 – 16h
Biologics

FIH dose selection for antibody-based therapeutics: A practical use case
Glenn Gauderat, Servier

16h – 16h30
Coffee break

16h30 – 17h
Vaccins

Vaccins toxicological pre-requisites to start a FIH with – kind of – serenity
Paul Desert, Sanofi

17h – 17h30
Survey - Wrap-up

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Friday 31st of May 2024
Espace Diderot, Paris 12ieme

FIH Workshop
Speakers

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Chasing optimum First-In-Human (FIH) dose:
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Introduction: Set up the scene on FIH dose selection: Regulatory environment and beyond

Virginie Boulifard, VP Non-Clinical Drug Safety Early Development, R&D, Ipsen

Virginie is graduated from the University of Paris VII Diderot in a PhD "Fundamental and Applied Toxicology. She is European and American Toxicology Board certified. She is an active member of the Pre-Clinical Expert group of EFPIA

She started her career in the pharmaceutical industry by working as a Toxicology research Scientist at Institut de Recherche sur la sécurité du médicament, RHONE-POULENC RORER (Vitry/seine) in collaboration with INSERM. She then started at Ipsen many years ago where she is currently VP Non-Clinical Drug Safety of Non-Clinical Drug Safety from January 2018 at Les Ulis/Paris-Saclay. She was temporarily relocated at Cambridge (Boston area). She leads non-clinical Safety strategies to support development and registration of Ipsen Portfolio in Rare Diseases, Oncology and Neurosciences.

Her professional interest is mainly in the non-clinical safety evaluation of compounds at ail stages from Research to Post-marketing, working closely with all the players of the Drug Development.

Selection of the FIM starting dose for a new NME is a critical aspect of early clinical development. Too high of a starting dose can put subjects at risk for serious toxicity. In contrast, too low of a starting dose can increase the number of dose cohorts required to reach the therapeutic range, which can increase risk by exposing more healthy volunteers (HVs) to the drug or deny potential benefit to patients by administering subtherapeutic doses, as well as increasing the overall time and expense of the development program.

Over the past 15 years, regulatory guidance shaped in part by adverse clinical trial events has led to the current approaches for FIH dose selection.

To assist in a data-driven and risk-based process for FIH starting dose selection, various factors such as safety, pharmacokinetics, and pharmacodynamics are integrated. Recently, novel factors such as Target Engagement, PK-PD Modeling, Patient Population Considerations, Adaptive Trial Designs and predictive modeling are considered. Moreover, key risk factors have been identified that help assign higher versus lower potential safety risk.

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Physiologically Based PharmacoKinetics (PBPK) for 1st in Human studies

François Bouzom, Director, PBPK, Simulations Plus

François Bouzom is currently director of the Simulation Studies Team at Simulations Plus Inc., where he leads and mentors scientists and provides consulting services for the pharmaceutical industry.

During more than 30 years, François has worked in the pharmaceutical industry to support drug development focusing on Pharmacokinetics and drug development. Through his different positions, he has built a strong knowledge of every skill linked to Pharmacokinetics, from non-clinical to clinical and from bioanalysis to modelling.

François has started working on PBPK modelling in 2000. From that time, he has never stopped working in that area, making people aware of its unique value, expanding its applications, and still having time to teach students.

The First In Human (FIH) study is a key study in the drug development. The purpose of FIH trials is to evaluate a potential new drug in humans for the first time, to study the human pharmacology, tolerability, and safety. Consequently, the non-clinical data in PD, PK and toxicology and their translation to human are important basis for planning and designing a FIH study.

Physiologically based pharmacokinetic (PBPK) modeling is routinely used during drug discovery for in-vitro to in-vivo translation and pharmacokinetic modeling in preclinical species. This can lead to the application of verified PBPK models for first-in-human (FIH) pharmacokinetic predictions.

The aim of this session will be to present, first, a consistent cross-industry strategy with integrated decision trees to highlight the value that appropriate use of PBPK modelling can add to FIH predictions for new chemical entities (NCE). Then, case study will be shared to allow the attendees to discuss and work together to anticipate the FIH study based on a non-clinical package.

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Strategies for dose selection of biotherapeutics in First-in-Human studies

Antoine Deslandes, Global Scientific Advisor PKDM, Sanofi

Currently Antoine Deslandes, has 2 roles at Sanofi. One role is in R&D, as Global Scientific Advisor in PKDM, as an expert of PK/PD of Therapeutic Proteins. His other role is within Manufacturing and Supply, in the Drug Device Integration unit, to support early application of subcutaneous devices and technologies in clinical projects.

First-in-human (FIH) trials are milestone bridges translating the lessons learned from preclinical studies to further clinical development phases. They are conducted primarily to determine the safe dose range for further clinical development. Regulatory guidelines provide a framework consisting in sequential parts: characterization of the pharmaco-toxicological effects in vitro and in animals, prediction of human exposure, prediction of human response, and mitigation of potential risks arising from unknowns and uncertainties. Therefore, selecting a FIH dose requires the integration of data from many disciplines. Additionally, study sponsors should evaluate several different approaches to the calculation of the safe starting dose and then take the most conservative approach.

By year-end 2022, the number of biologic approvals outpaced that of small-molecule new molecular entities. The therapeutic biologics pipeline is changing, as companies are developing new modalities for a diverse array of molecular targets. Case studies and lessons learned on these new translational challenges will be discussed.

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FIH dose selection for antibody-based therapeutics: a practical use case

Glenn Gauderat, Pharmacometrician, Servier

Glenn Gauderat is a Pharmacometrician at Servier. Specializing in antibody-based therapeutics within Servier's translational pharmacometric department, Glenn provides PK/PD support to projects across multiple therapeutic areas from research to early clinical phases. He holds a master's degree in biotechnology and a PhD in pharmacokinetics.

Clinical dose selection for antibody-based therapeutics requires expertise from multiple disciplines and involves the use of many different data sources. The strategy for clinical dose selection is established in a case-by case basis and may vary depending on the antibody (Ab) format, the mode of action, the target and the data available.

The goal of this session will be to share views and experiences around first-in-human dose selection strategy for Abs.

The session will start with a general presentation about the pharmacokinetics and pharmacodynamic properties of Abs followed by discussions around several case studies (fictional or not). Each case study will begin with a short presentation of the question and the associated context and data package. Discussions will then be organized in small groups of participants.

We will address common questions, from high/strategic level to more technical level topics such as:

- Establishing a starting dose rationale from a given data package
- Dose selection strategy for soluble targets
- Selection of *in vitro* data to use for FIH starting dose
- How to define the maximal dose to be tested in the FIH trial
- Prediction of receptor occupancy (RO) : which assay to use (cell-based RO vs surface plasmon resonance…)
- How to deal with uncertainty regarding target concentrations

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Vaccins toxicological pre-requisites to start a FIH with - kind of - serenity

Paul Desert, Head of Nonclinical Safety Global Immunology

Paul Desert is a Toxicologist expert working at Sanofi R&D, where he is heading the Non-Clinical Safety Department of the Vaccine Division. His work focuses in managing a team of toxicologists and ensuring that the Non-Clinical Safety strategies are the best ones to support initiation of clinical trials and/or licensure of new vaccines. He and his team also provide support to Sanofi Pharma R&D anti-infectious disease projects, Manufacturing & Supply activities. He is also responsible for the animal facilities at the Marcy l'Etoile site, Lyon, where immunogenicity & efficacy studies are conducting, managing the entire team. Altogether, Paul and his teams are responsible for establishing a strategy to animal use for the Vaccines R&D, as well as promoting innovative approaches to direct animal experimentation, such as in silico, in vitro, digital and other alternative models; the objective is to increase the robustness of the predictivity of vaccine safety to human.

Paul is a Doctor of Pharmacy (School of Pharmacy, Rouen, France) and he holds two Master's Degrees in Toxicology and in Biological and Medical Sciences (University of Paris V & XI and School of Pharmacy, Rouen) with more than 20 years of experience as Toxicologist in the Pharmaceutical Industry. He is board member of the French Society of Toxicology. Before joining Sanofi, he worked at Citoxlab (now Charles River, Evreux, France) as Study Director managing any kind of toxicology studies for pharmaceuticals and chemicals, and at Solvay Pharmaceuticals/ Abbott Products GmbH, Hannover, Germany) as project toxicologist for early-stage projects in the cardiovascular therapeutic area. He also elaborated a global early toxicity testing strategy for the Group and he was the Principal Investigator for two consortia aiming at predicting early cardiotoxicity liabilities of new drug candidates.

Vaccine toxicology pre-requisites have evolved a lot in a short period of time, together with the regulatory environment framing the toxicology study designs, study types and non-clinical safety expectations to support dosing in humans safely. With the COVID-19 pandemic, the new area of mRNA/LNPs vaccine approaches is taking an increasing proportion of the prophylactic and therapeutic vaccine assets developed by the pharmaceutical industry.

This novel approach contains some specificities with regard to the toxicological support needed to ensure safe progression of the vaccine candidates throughout the development path. During this presentation, we will go through current non-clinical safety expectations to support the development of conventional and mRNA/LNPs vaccine candidates and be on a safe side at the time a first subject is being injected in a Phase I clinical trial.

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