Association Française de Pharmacologie Translationnelle
Le Club Phase 1

EUFEMED European Federation for Exploratory Medicines Development

HEALTHI université PARIS-SACLAY
Interdisciplinary Action Health and Therapeutic Innovation

Course: "Pre-Clinical And Clinical Safety In Early Development Human Trials"

13-17 March 2023 – 5 days in Paris-Saclay University, France

Day 1: Monday 13-March-2023

Minimal non-clinical safety package to support the first dose in human

09:00 – 09:15	**Introduction of faculty and participants – Overview on training course** Coordinator: Henri Caplain, Clinical Pharmacologist, Senior Advisor in Early Clinical Development, Translational Pharmacology, and Drug Safety Risk Management, President AFPT-Le Club Phase 1
09:15 – 11:15	**Design, conduct and interpretation of general and reproductive toxicology studies** Learning objectives: To provide an understanding/knowledge of general and reproductive toxicology evaluation supporting the first dose in human. Key concepts: Design of general and reproductive toxicology studies; Dose and species selection; Safety ratio/safety margin; No Observed Effect Level/No Observed Adverse Event Level (NOAEL); Lowest Observed Adverse Effect Level (LOAEL); Maximal Tolerated Dose (MTD); Maximum Feasible Dose (MFD); Limit doses/exposures in repeated -dose toxicity studies; Target organs; Relevance of animal models, including target expression, pharmacodynamics, metabolism and PK aspects, and off-target binding activities and receptor/ligand occupancy and kinetics; Micro-dosing and sub-therapeutic dose concepts and limitations; Juvenile animal testing; Duration of studies to support clinical trials and marketing approval. Speaker: Philippe Detilleux, Global Head, Preclinical safety, Sanofi R&D
11:15 – 11:30	Coffee Break
11:30 – 13:00	**Pharmacology studies** Learning objectives: To provide an understanding/knowledge of pharmacodynamic and safety pharmacology evaluation supporting the first dose in human. Key concepts: Primary pharmacodynamic studies (*in vitro* and/or *in vivo*); Design of safety pharmacology studies; Core battery systems; Assessment of effects on cardiovascular, respiratory and central nervous systems (CNS); Supplemental and follow-up safety pharmacology studies; Secondary organ systems of interest; Use of in silico, animal- and cell-based models of disease mechanisms to study the pharmacology of a new drug. Speaker: Stephanie Plassman, Specialist in Veterinary Pharmacology and Toxicology, AGAH Regent
13:00 – 14:00	Lunch

14:00 – 16:00	**The use of nonclinical pharmacology and pharmacokinetic assessments; PK/PD modelling to bridge nonclinical and clinical safety endpoints** Learning objectives: To provide an understanding/knowledge of nonclinical pharmacology and pharmacokinetic evaluation supporting the first dose in human and PK/PD modelling to bridge nonclinical and safety endpoints. Key concepts: Assessment of the mode of action/effects of candidate compound on the target; Absorption/distribution/ metabolism and excretion (ADME) assessment; Toxicokinetic evaluation; Half-life, C_{max}, systemic exposure (AUC), in vitro metabolic and plasma protein binding for animals and humans, clearance, volume of distribution, intrinsic and extrinsic factors which affect the PK; PK linearity/non-linearity/ Dose-proportionality; Steady-state; Accumulation factors; Metabolites assessment (animals and nonclinical characterization for humans); Pharmacogenetics/polymorphisms/ Pharmacometrics/PK/PD modelling. Speaker: Jeremy Perrier, PBPK scientist, PhinC Development
16:00 – 16:15	Coffee Break
16:15 – 18:15	**On- and off-target binding affinities** Learning objectives: To provide an understanding/knowledge of on- and off-target evaluation before the first use in human. Key concepts: On- and off-target binding affinities; Receptor/ligand occupancy and kinetics. Speaker: Friedemann Schmidt, Computational / Systems Toxicologist, Sanofi R&D and Technical University Darmstadt
18:15	Adjourn

Day 2: Tuesday 14-March-2023

Minimal non-clinical safety package to support the first dose in human and principles of risk assessment from non-clinical safety package

09:00 – 10:30	**Immunotoxicity assessment** Learning objectives: To provide an understanding/knowledge of evaluation of potential immunotoxicity. Key concepts: Standard toxicity studies; Study design to assess drug-induced immunotoxicity; Selection of assays; Potential immunotoxicity linked to the pharmacological properties, intended patient population, structural similarity, disposition of the drug. Speaker: Pr. Marc Pallardy, Dean Faculty of Pharmacy and Director of Interdisciplinary Action "Health and Therapeutic Innovation" Paris-Saclay University
10:30 – 10:45	Coffee Break
10:45 – 12:15	**Nonclinical studies required before first clinical use of gene therapy medicinal product** Learning objectives: To provide an understanding/knowledge of nonclinical package require before the first use in human of gene therapy medicinal product. Key concepts: Pharmacodynamic "proof of concept" in nonclinical model(s); Biodistribution; Studies to establish dose; Toxicity studies for the whole gene therapy medicinal product (virus or other micro-organism or vector particle and/or delivery system + expression vector including cassette + transgene; Integration studies; Germline transmission; Target tissue selectivity; Immunogenicity and immunotoxicity; Delivery devices and excipients; Environmental risk/shedding. Speaker: Philippe Detilleux, Global Head, Preclinical safety, Sanofi R&D
12:15 – 13:15	Lunch
13:15 – 14:15	**Genotoxicity assessment** Learning objectives: To provide an understanding/knowledge of genotoxicity evaluation supporting the first dose in human and potential genotoxic impurities. Key concepts: Design of genotoxicity assessment; *In vitro* and *in vivo* testing; Genotoxic impurities and threshold of toxicological concern (TTC). Speaker: Guy Bouvier, Toxicology and Product Safety Director, Pierre-Fabre Laboratories
14:15 – 15:15	**Phototoxicity assessment** Learning objectives: To provide an understanding/knowledge of photosafety testing before the first use in human. Key concepts: Phototoxicity; Photoallergy; Photogenotoxicity; Photocarcinogenicity; Need for photosafety testing before first in human study; Phototoxicity testing. Speaker: Béatrice Gauthier, Veterinary Pathologist Expert, Sanofi R&D

15:15 – 16:15	**Nonclinical local tolerance assessment** Learning objectives: To provide an understanding/knowledge of nonclinical local tolerance evaluation. Key concepts: Design and need of local tolerance studies; Sensitizing potential; Oral, ocular, cutaneous tolerance testing; Transdermal systems; parenteral tolerance testing; Rectal and vaginal tolerance testing. Speaker: Béatrice Gauthier, Veterinary Pathologist Expert, Sanofi R&D
16:15 – 16:30	Coffee Break
16:30 – 18:30	**Principles of risk assessment from nonclinical studies, critical review of scientific literature and early clinical data; risk factors** Learning objectives: To provide the principles behind the principal of risk assessment from nonclinical studies. Key concepts: Importance of toxicokinetic; Risk factors/Safety factor; PK linearity/nonlinearity/dose proportionality/accumulation; Variable bioavailability; Steep dose response curve; Severe toxicities; Non-monitorable toxicities; Reversible/Irreversible toxicities; Toxicities without premonitory signs; Long-lasting binding and effects; Nature of the target and novel therapeutic targets; Differences and similarities between the pharmacology and toxicology of compounds and their metabolites in animals, humans, and cell preparations that provide qualitative and quantitative assessment: genotoxicity, general toxicity, toxicokinetics, pharmacokinetics, drug metabolism, safety pharmacology, immunotoxicity, reproductive toxicity, carcinogenicity; Relevance of nonclinical findings in various organ systems (liver, CNS, endocrine, eye, kidney, reproductive and gastrointestinal tract); Extrapolation of animal findings to human; Differences in nonclinical safety and toxicity packages between small molecules, biological medicines, advanced therapies. Speaker: Nigel Roome, Toxicology and Toxicologic Pathology Senior Consultant
18:30	Adjourn

Day 3: Wednesday 15-March-2023
Safety in human pharmacology trials

09:00 – 10:30	**First-in-human trials and Management of Medical Emergencies** Learning objectives: To provide an understanding/knowledge of how to perform a safe first-in-human study. Key concepts: How to read and understand the safety concerns in the first Investigators Brochure (IBs) and its maintenance; General principles of first-in-human studies, including overall design; Estimating the first safe dose in a first-in-human trial, including the concepts of Human Equivalent Dose (HED), Maximum Recommended Starting Dose (MRSD), NOAEL-based approach, Minimal Anticipated Biological Effect (MABEL), Minimum Effective Dose (MED), Pharmacological Active Dose (PAD); Allometric scaling; Sequence and interval between dosing of subjects within the same cohort, concept of sentinel subjects; Safe dose escalation scheme and last dose, including the Anticipated Therapeutic Dose Range (ATD); Minimal clinical evaluations and evaluations depending on the nonclinical findings, including the intensity and duration of monitoring; Safety biomarkers; Stopping rules; How to proceed from single ascending dose to multiple ascending dose – assessment evaluation of SAD safety and PK data, integrated protocols versus consecutive trials (pros, cons and operations); Maximum duration of treatment; Decision making group or safety review committee; Identification of protocol violations and deviations; Safety data: tables and graphs for the evaluation of adverse events, laboratory data and other data related to safety; PD data: tables and graphs for the evaluation of pharmacodynamic. Speaker: Yves Donazzolo, Principal Investigator Optimed/Eurofins, AFPT-Le Club Phase 1, Past-President EUFEMED
10:30 – 10:45	Coffee Break
10:45 – 11:45	**First-in-human trials and Management of Medical Emergencies** Learning objectives: To provide an understanding/knowledge of how to perform a safe first-in-human study. Key concepts: How to read and understand the safety concerns in the first Investigators Brochure (IBs) and its maintenance; General principles of first-in-human studies, including overall design; Estimating the first safe dose in a first-in-human trial, including the concepts of Human Equivalent Dose (HED), Maximum Recommended Starting Dose (MRSD), NOAEL-based approach, Minimal Anticipated Biological Effect (MABEL), Minimum Effective Dose (MED), Pharmacological Active Dose (PAD); Allometric scaling; Sequence and interval between dosing of subjects within the same cohort, concept of sentinel subjects; Safe dose escalation scheme and last dose, including the Anticipated Therapeutic Dose Range (ATD); Minimal clinical evaluations and evaluations depending on the nonclinical findings, including the intensity and duration of monitoring; Safety biomarkers; Stopping rules; How to proceed from single ascending dose to multiple ascending dose – assessment evaluation of SAD safety and PK data, integrated protocols versus consecutive trials (pros, cons and operations); Maximum duration of treatment; Decision making group or safety review committee; Identification of protocol violations and deviations; Safety data: tables and graphs for the evaluation of adverse events, laboratory data and other data related to safety; PD data: tables and graphs for the evaluation of pharmacodynamic data. Speaker: Yves Donazzolo, Principal Investigator Optimed/Eurofins, AFPT-Le Club Phase 1, Past-President EUFEMED

11:45 – 12:30	**Management of Medical Emergencies** Learning objectives: To provide the principles of the management of medical emergencies in human pharmacology trials. Key concepts: Pre-trial interviews and screening procedures; Up-to-date resuscitation procedures and guidelines; Diagnosis and management of anaphylaxis and other severe allergic phenomena, cardiac arrhythmias, respiratory emergencies, syncope, convulsions and other neurotoxicity. Speaker: Yves Donazzolo, Practitioner Emergency Department, Grenoble University Hospital, AFPT-Le Club Phase 1, Past-President EUFEMED
12:30 – 13:30	Lunch
13:30 – 14:30	**Selection of study population for the first-in-human trial** Learning objectives: To provide an understanding/knowledge of choice of study population for the first-in-human trial. Key concepts: Healthy participants versus patients; Inclusion of special population including women, children, elderly, ethnicity, genotype(s), cultural differences, possible interaction with subject's lifestyle, e.g. smoking, use of alcohol or drugs; Use of other medications with the possibility for adverse reactions and/or difficulties in the interpretation of results; Safety criteria of inclusion and exclusion; How to exclude participants with drug abuse and drug dependence; Protection of research participants; Sponsor and investigator responsibilities in context of trial participants, in particular, to avoid conflicts of interest. Speaker: Lionel Hovsepian, Clinical Pharmacologist, Early development expert, AFPT-Le Club Phase 1
14:30 – 14:45	Coffee Break
14:45 – 16:30	**First-in-human oncology trials** Learning objectives: To provide an understanding/knowledge of first-in-human oncology trials. Key concepts: Trials design, including traditional 3+3 design, Continual Reassessment Method (CRM), Dose Escalation with Overdose Control (EWOC) and other Bayesian approaches; Phase I trials of Agent Combinations; First dose; Dose escalation; Stopping rules; Grading of adverse events including the 'Common Terminology Criteria for Adverse Events' (CTCAE) descriptive terminology; Maximal Tolerated Dose (MTD; Dose limiting toxicities (DLTs); Data safety monitoring board (DSMB). Speaker: Pr. Christophe Massard, Medical Oncologist, Centre Eugene Marquis Rennes

16:30 – 18:30	**Other Phase I trials: Food effect, Bioavailability, Drug-drug interactions, patients with renal or hepatic impairment, TQT studies** Learning objectives: To provide an understanding about the timing and safety implications of other Phase I trials, how to assess safety findings and individual exposure and an understanding/knowledge of the integrated cardiac safety. Key concepts: Safe food effect trial; Bioequivalence study; Drug-drug interactions to be performed in Phase I of clinical development; Patients with renal or hepatic impairment; Design and timing of TQT study; Integrated cardiac safety concept. Speaker: Denis Gossen, Clinical Pharmacologist, AFPT-Le Club Phase 1
18:30	Adjourn

Day 4: Thursday 16-March-2023 – Pharmacovigilance in human pharmacology trials

09:00 – 10:30	**Adverse events (AEs)/Adverse drug reactions (ADRs) evaluation and reporting** Learning objectives: To provide an understanding/knowledge of AEs/ADRs evaluation and reporting. Key concepts: Role of the pharmaceutical professional in drug safety and pharmacovigilance; Methodology for collection in clinical trials, including reporting; Mechanisms of AEs/ADRs/safety risks; Assessment and classification of adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), adverse events of special interests (AESIs);.MedDRA coding and classification; Medical aspects of AEs/ADRs, including principles of event attribution, evidence for association and causality, expectedness and seriousness assessments; The extent of variation in normality. Speaker: Hervé Bester, VP Global Patient Safety – Rare Diseases Therapeutic Area Head, Ipsen
10:30 – 10:45	Coffee Break
10:45 – 12:15	**Adverse events (AEs)/Adverse drug reactions (ADRs) evaluation and reporting (Cont'd)** Learning objectives: To provide an understanding/knowledge of.AEs/ADRs evaluation and reporting. Key concepts: Role of the pharmaceutical professional in drug safety and pharmacovigilance; Methodology for collection in clinical trials, including reporting; Mechanisms of AEs/ADRs/safety risks; Assessment and classification of adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), adverse events of special interests (AESIs);.Medical aspects of AEs/ADRs, including principles of event attribution, evidence for association and causality, expectedness and seriousness assessments; The extent of variation in normality. Speaker: Hervé Bester, VP Global Patient Safety – Rare Diseases Therapeutic Area Head, Ipsen
12:15 – 13:15	Lunch
13:15 – 14:45	**Severity of adverse events (AEs), adverse drug reactions (ADRs)** Learning objectives: To illustrate the potential safety impact of AEs/ADRs. Key concepts: General tolerability; Tolerance; Liver/renal toxicity, including drug-induced liver injury (DILI); CNS toxicity; Cardiac toxicity, including pro-arrhythmogenic risk; Immune toxicity, including cytokine release syndrome (CRS); Other system or local toxicities of concern; Monitoring of vital signs; What happens in case of pregnancy during a trial; Predisposing factors and the impact of pre-existing disease on the susceptibility for and severity of adverse events. Speaker: Henri Caplain, Clinical Pharmacologist, Senior Adviser in Early Clinical Development, Translational Pharmacology, and Drug Safety Risk Management, President AFPT-Le Club Phase 1
14:45 – 15:00	Coffee Break
15:00	**Development Safety Update Report in Phase I clinical development**

– **16:30**	Learning objectives: To provide an understanding/knowledge of how read and fill a development safety update report after the first Phase I clinical trials. Key concepts: Rational for writing DSURs; ICH E2F and CIOMS V; Assessment process; DSUR outcomes; Compliance; Benefit/risk balance assessment concept. Case study(ies) Speaker: Henri Caplain, Clinical Pharmacologist, Senior Adviser in Early Clinical Development, Translational Pharmacology, and Drug Safety Risk Management, President AFPT-Le Club Phase 1
16:30 – **18:30**	**Risk management plan in early drug development** Learning objectives: To provide the principles of the risk management plan in early drug development. Key concepts: Risk concept; Crisis management; Impact of AE on drug development and further trials; Risk management plan and planning; Risk evaluation and mitigation strategy; Safety specifications; Important identified and potential risks, missing information; Risk assessment; Risk minimization activities; Risk communication; Effectiveness of risk minimization; DRMP/DSUR progression during drug development; How to fill a risk management plan prior to the CTA/IND. Case study(ies) Speaker: Henri Caplain, Clinical Pharmacology, Senior Adviser in Early Clinical Development, Translational Pharmacology, and Drug Safety Risk Management, President AFPT-Le Club Phase 1
18:30	Adjourn

Day 5: Friday 17-March-2022 – Case Studies on Risk Management in human pharmacology trials and exam

09:00 – 10:30	**Case Studies** Work by sub-group on a case study Facilitator: Henri Caplain, Clinical Pharmacology, Senior Adviser in Early Clinical Development, Translational Pharmacology, and Drug Safety Risk Management, President AFPT-Le Club Phase 1
10:30 – 10:45	Coffee Break
10:45 – 12:30	**Case Studies** End and reporting Facilitator: Henri Caplain, Clinical Pharmacology, Senior Adviser in Early Clinical Development, Translational Pharmacology, and Drug Safety Risk Management, President AFPT-Le Club Phase 1
12-30 - 13:00	**Training debriefs and Summary** Facilitator: Henri Caplain, Clinical Pharmacology, Senior Adviser in Early Clinical Development, Translational Pharmacology, and Drug Safety Risk Management, President AFPT-Le Club Phase 1
13-00 - 14:00	Lunch
14:00 - 16:00	**Exam** 1) Selection of multiple-choice questions (1 hour): 60% of questions must be correctly answered to pass test and receive a certificate. 2) Short questions (4 of 15 minutes each): 10/20 must be obtained to pass test and receive a certificate
16:00	**End of the training**