Centre de Congrès de Lyon
Lyon, France
15-17 May 2019

FINAL PROGRAMME AND ABSTRACT BOOK

THE CHANGING LANDSCAPE OF EARLY MEDICINES DEVELOPMENT: BE PREPARED

EUROPEAN FEDERATION FOR EXPLORATORY MEDICINES DEVELOPMENT

CONTENTS

WELCOME

Dear Colleague,

It is our great pleasure to welcome you to the 2nd conference of the European Federation for Exploratory Medicines Development (EUFEMED)!

This conference is the result of a continued effort of EUFEMED to gather all stakeholders of early clinical drug development to evaluate and discuss recent developments in the field. We are proud to present to you our exciting scientific programme for 2019 entitled: **The changing landscape of early medicines development: be prepared!**

This two-day meeting will include a mixture of focused scientific sessions, interactive workshops and open forum discussions.

Two-parallel, pre-conference workshops will take place on Wednesday 15 May 2019 and are dedicated to **'Modelling and simulations, including PBPK to improve the clinical development'** and **'Early clinical development of biologics – what is so different about it?'**

The Welcome Reception will take place in the Exhibition Hall immediately after these workshops finish.

It is our intention to offer a stimulating scientific atmosphere where you can meet old colleagues, make new friends and contacts, inspired by the lively city of Lyon.

We welcome you to EUFEMED 2019!

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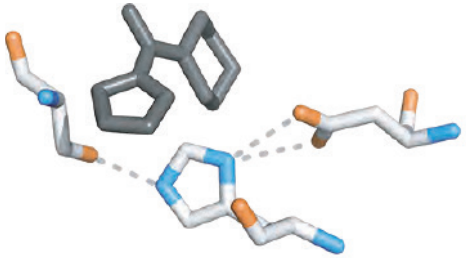
Jan de Hoon
EUFEMED Secretary

Steffan Stringer
Communications Lead

ABIDE THERAPEUTICS



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ABOUT EUFEMED

The European Federation for Exploratory Medicines Development (EUFEMED) was founded in 2015 as a result of an ongoing, informal collaboration between several European societies active in the area of human pharmacology.

The founding members of EUFEMED are:

Belgian Association for Phase I Units (BAPU)

CLUB PHASE 1

Association for Applied Human Pharmacology (AGAH)

Association for Human Pharmacology in the Pharmaceutical Industry (AHPPI)

To find out more about EUFEMED visit www.eufemed.eu

EUFEMED Office
Rue de l'industrie 4
1000 Brussels
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VENUE

Venue address:
Centre de Congrès de Lyon
50 Quai Charles de Gaulle
69463 Lyon cedex 06
France

Website: www.ccc-lyon.com

The conference will take place in the following areas:

Parc Walkway	Registration desk, CPD register and cloakroom
Commission Room Rhone 1 **Commission Room Rhone 2**	Pre-Conference Workshop 1 Pre-Conference Workshop 2
Pasteur Auditorium	Plenary sessions
Pasteur Auditorium **Commission Room Rhone 1** **Commission Room Rhone 2** **Commission Room Rhone 3a**	Breakout sessions
Rhone Upper Square	Exhibitor and catering poster display and catering
Pasteur Lounge	Poster display and catering
Commission Room Rhone 5	Speaker preview

GENERAL INFORMATION A-Z

ABSTRACTS

A copy of all the conference abstracts are included in this Final Programme and Abstract Book. All presented abstracts will be available to download online as an e-book published by Frontiers in Pharmacology. The link will be published on the EUFEMED website www.eufemed.eu after the conference. All attendees will be notified when they become available.

This Final Programme and Abstract Book will also be published on the EUFEMED website www.eufemed.eu.

ACCESS

Centre de Congrès de Lyon is fully accessible by wheelchair to all public areas by ramp or lift. If you have any special access requirements, please advise the Conference Secretariat at the registration desk.

ACCREDITATION

The Faculty of Pharmaceutical Medicine has approved the conference for Continuing Professional Development (17.5 hours). Delegates must sign the register of attendance, for each day that they attend the conference in order to receive CPD points. The register will be available at the registration desk.

AWARDS

Best oral and best poster presentations will be awarded. The top three winners of each category will be presented at the Conference Dinner on Thursday evening.

BADGES

For security reasons name badges must be worn at all times as these serve as the admission pass to all scientific sessions and the exhibition.

CERTIFICATES OF ATTENDANCE

Certificates of Attendance will be issued to all delegates via email after the conference.

CONFERENCE SECRETARIAT

Should you have any queries relating to the conference, please do not hesitate to get in touch with the Conference Secretariat at the registration desk.

The Conference Collective Ltd
8 Waldegrave Road, Teddington, Middlesex TW11 8HT, UK
Tel: +44 (0) 20 8977 8997
Email: eufemed@conferencecollective.co.uk

Conference Collective

CLOAKROOM

A cloakroom facility is available throughout the conference in the Parc Walkway. There is no cover charge to use the cloakroom. Attendees are permitted to leave luggage in the cloakroom.

CONFERENCE CATERING

Refreshments and lunch will be available for conference attendees in Rhone Upper Square which is located in the exhibition area. An additional catering point will be located in the Pasteur Lounge on Thursday. Catering is included in your registration fee. For catering timings, please see the conference programme on pages 14, 15, 23 and 24.

DELEGATE FEEDBACK

After the conference, all delegates will receive an electronic feedback form via email. We really do value your comments so please take a few minutes to complete this information to help us plan for future EUFEMED events.

EMERGENCIES AND EVACUATION PROCEDURES

Fire exits are indicated prominently in all rooms and corridors. There are no planned fire drills during the EUFEMED conference.

EXHIBITION

There is an exhibition being held alongside the conference programme, with companies and CROs all available to talk to you during the following times:

Wednesday 15 May	18.15 – 19.30 (Welcome Reception)
Thursday 16 May	08.00 – 17.30
Friday 17 May	08.30 – 15.00

Please take time to visit the exhibiting companies during the breaks, as their support is integral to the success of the conference.

INSURANCE

EUFEMED and the Conference Secretariat do not accept responsibility for individual medical, travel or personal insurance and delegates are advised to take out their own insurance policies.

MOBILE PHONES AND ELECTRONIC DEVICES

As a courtesy to speakers and your fellow delegates, you are kindly asked to restrict mobile devices use during sessions for social media use and please ensure all devices are switched to silent. Video, audio and photographic recording of presentations on any device is not permitted.

PARALLEL BREAKOUT SESSIONS – THURSDAY 16 & FRIDAY 17 MAY

The four parallel breakout sessions scheduled on Thursday 16 May will be repeated on Friday 17 May. Spaces at these sessions are limited, so if you miss your preferred session on Thursday you will have the opportunity to attend on Friday.

Scheduled timings for the parallel breakout sessions:

Thursday 16 May	16.00 – 17.30
Friday 17 May	10.45 – 12.15

The parallel breakout sessions will be located in the following rooms:

Pasteur Auditorium
Commission Room Rhone 1
Commission Room Rhone 2
Commission Room Rhone 3A

PHOTOGRAPHY

Please note that photography will be taking place throughout the conference, and that some sessions may be filmed. These images and recordings may be used by EUFEMED for promotional purposes. If you have any queries about this please visit the registration desk.

POSTERS

Mounting and Removal of Posters.

If the poster presenter is unable to meet the set-up or removal times, please arrange for a co-author or other colleague to assist with set-up and/or removal. Adhesive will be available on each board.

Mounting of Posters

Thursday 16 May	Posters should be mounted between 08.00 – 08.30

Removal of Posters

Friday 17 May	Posters should be removed between 15.00 – 15.30 hrs (following the close of the conference).

We regret that we are unable to forward posters to authors following the conference. Any posters remaining on boards after 15:30 on Friday will be discarded.

Storage of Poster Tubes

Please do not leave your tube by the poster board as it presents a health and safety hazard. Please leave your poster tube in the cloakroom. All poster presenters should ensure their poster tubes are clearly labelled for identification purposes with your name and poster number.

GUIDED POSTER TOURS

Thursday 16 May - 13.45 - 14.15

On Thursday 16 May, all presenting authors are requested to stand by their poster board from 13:45 - 14.15. During this time, there will be three parallel tours, each conducted by two guides. The guides will spend 6 minutes at each poster allowing 3 minutes for the author to make a short presentation, followed by 3 minutes for questions. Posters of oral presentations will not be discussed by poster guides. Delegates are encouraged to join to listen to the discussions between guides and authors.

PRE-CONFERENCE WORKSHOPS

Two parallel, pre-conference workshops have been scheduled on Wednesday 15 May at 11.00 - 18.15 and are dedicated to **'Modelling and simulations, including PBPK to improve the clinical development'** and **'Early clinical development of biologics - what is so different about it?'**

Commission Room Rhone 1	**Workshop 1:** Modelling and simulations, including PBPK to improve the clinical development
Commission Room Rhone 2	**Workshop 2:** Early clinical development of biologics – what is so different about it?

QUESTIONS TO SPEAKERS

During discussion periods, delegates who wish to pose a question should raise their hand clearly and wait to be acknowledged by the Chairperson. Please wait until you have been given a microphone and then give your name and affiliation before asking a question.

REGISTRATION DESK

If you have any queries during the conference, please enquire at the Registration desk where a member of the Conference Secretariat will be pleased to assist.

The Registration desk opening hours:

Wednesday 15 May	10.00 – 11.00 Registration for Pre-Conference Workshop attendees only
	18.15 – 19.30 Registration for conference attendees
Thursday 16 May	08.00 – 17.30
Friday 17 May	08.00 – 15.00

SOCIAL MEDIA

Delegates are encouraged to tweet ideas, debate and chat or to send comments at #eufemed2019 during the conference.

SOCIAL PROGRAMME

Welcome Reception

The Welcome Reception provides the first opportunity of the conference to catch up with friends, meet exhibitors and network with fellow delegates. The Welcome Reception is included in the registration fee for all participants.

Wednesday 15 May	18.15 – 19.30	Rhone Upper Square - Exhibition Area

Conference Dinner

Thursday 16 May	19.30 – 23.00	Hermès River Boat - 16 Quai Claude Bernard, 69007, Lyon, France

Tickets should have been booked and prepaid in advance of the conference. If you pre-booked a ticket, you should have received it with your name badge upon arrival at the conference.

If you wish to purchase a ticket during the conference, please speak to a member of staff at the Registration desk who can advise about availability.

Dinner tickets cost €80 (plus VAT) which includes the pre-dinner drinks reception.

The boarding/landing dock for the Hermès River Boat is located opposite Centre de Congrès de Lyon. The boat will depart from 16 Quai Claude Bernard, Lyon France from 19.30, departing at 20.15. It will not be possible for late comers to join us for the dinner once the boat has departed. The boat will arrive back to the boarding address at 23.00.

Dress code for the conference dinner is smart casual.

SPEAKER PREVIEW

All presenters must download their presentation at the technician's desk, in the speaker preview room (Commission Room Rhone 5) at least two hours before the start of your session.

Slides will be downloaded to the organisers laptop with presenters advancing their slide via a slide-advancer (with integrated laser pointer).

ARRIVING FOR YOUR PRESENTATION

Please arrive at the room where you are due to present at the latest 10 minutes before the start of the session. Make yourself known to the technician at the lectern who will familiarise you with the audio-visual controls.

Please also make yourself known to the Chairpersons and take a seat at the front of the auditorium where seats will be reserved for speakers.

WI-FI

Wi-Fi is available throughout the venue.

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PRE-CONFERENCE WORKSHOP: WEDNESDAY 15 MAY 2019

Workshop 1: Modelling and simulations, including PBPK to improve the clinical development
Chairs: Andreas Kovar, Germany and François Bouzom, Belgium

10.00-11.00	**Registration**
11.00	**Welcome and introduction by the Chairs** Henri Caplain, France
11.15	**Principles of modeling and simulation including physiology-based pharmacokinetic (PBPK)** François Bouzom, Belgium
11:45	**A general in-silico framework for maximizing the benefit-risk ratio of a treatment** Roberto Gomeini, France
12.30	Lunch
13.15	**Simulation of first-in-human using an allometrically scaled population mechanistic TMDD model** Géraldine Ayral, France
13.45	**From phase I data to phase II trial design: simulation and extension of a population pharmacokinetic model** Pauline Traynard, France
14.15	**How PBPK modelling together with Bayesian statistics and targeted clinical data can be used to predict drug pharmacokinetics across patient populations?** Lars Kuepfer, Germany
14.45	**Various examples for the integration of cellular effect models from computational systems biology into whole-body PBPK models** Lars Kuepfer, Germany
15.15	Refreshment break
15.45	**Population-based and physiology-based PK models for drug-drug interaction trials and trials waiver** Kenichi Umehara, Switzerland
16.30	**Advance current PBPK model applications to support internal development and regulatory decisions** Maxime Le Merdy, Switzerland
17.00	**How to obtain biowaivers for clinical trials using PBPK, two case studies** Maxime Le Merdy, Switzerland
18.00	**What did we learn?** Open forum discussion with speakers and participants
18.15	End of Workshop 1
18.15-19.30	**Welcome Reception - Exhibition Area, Centre de Congrès de Lyon**

Workshop 2: Early clinical development of biologics – what is so different about it?

Chairs: Hildegard Sourgens, Germany and Jan de Hoon, Belgium

10.00-11.00	**Registration**
11.00	**Welcome and introduction by the Chairs**
11.10	**New therapeutic concepts** Philip Barrington, UK
12.45	Lunch
13.30	**What is different in PK of biologicals** Stephan Glund, Germany
15.00	Refreshment break
15.15	**How to approach PD and safety** Meagan O'Brien, US
16.45	**ADAs / Immunogenicity** Ann Gils, Belgium
17.45	**What did we learn?** Open forum discussion with speakers and participants
18.15	End of Workshop 2
18.15-19.30	**Welcome Reception – Exhibition Area, Centre de Congrès de Lyon**

PRE-CONFERENCE WORKSHOP SPEAKER BIOGRAPHIES

Dr Géraldine Ayral – Lixoft, France

Géraldine Ayral is a multidisciplinary scientist with a main interest in pharmacometrics.

She joined Lixoft in 2016 as VP Applications, where she is in charge of the technical support, trainings and demonstrations, product specification as well as the technical communication. Geraldine holds an engineering degree from Ecole Polytechnique (Paris, France) and a Master in computational biology from ETH Zürich (Switzerland). After an experience as assistant project manager at SoBios, a start-up developing software for modeling and in silico simulation, she started a PhD in systems biology and multi-scale modeling at INRIA Paris. She received her doctoral degree in 2016.

Dr Philip Barrington - Faculty of Pharmaceutical Medicine, UK

Philip has worked in Early Clinical Development for 30 years, starting in CRO's before joining Glaxo as Head of their Internal Clinical Pharmacology Unit. Philip spent 3 years working for a Biotech company and 15 years at Eli Lilly.

Philip has extensive experience of working with small molecules and Biopharmaceutics (monoclonal and bispecific antibodies, fusion proteins, Pegylated peptides and antibody-drug conjugates) and has worked in the majority of therapeutic areas. His main areas of interest are autoimmune diseases, diabetes, biomarker development and medical devices. Philip also has broad experience of the application of PK/PD modelling and simulation to early phase development.

Philip is currently a member of the Faculty of Pharmaceutical Medicine's Board of Examiners.

Mr François Bouzom - UCB Biopharm, Belgium

François Bouzom, pharmacist by training at the University Paris XI, works in the pharmaceutical industry from 25 years, especially in the Pharmacokinetics area. Starting as study director, François developed his skills in PK and PK/PD modelling, including population approach, both in non-clinical and clinical development.

Since 2000, François is actively working in PBPK (Physiologically Based PharmacoKinetic) modeling to integrate that approach in the drug development, to develop its use in the pharmaceutical industry and for its acceptance as a powerful tool for regulatory assessment.

Between 2009 and 2015, François was Head of non-clinical Pharmacokinetics & modelling Department in Servier Laboratories (Orléans). Built from scratch, the department was designed to support the non-clinical PK studies including the bioanalysis, the distribution studies including the Mass Spectrometry Imaging (MSI) and some non-clinical PK and PBPK modelling support.

Since 2015, François is Director, non-clinical PK/PD in UCB Biopharma in Belgium. He is involved in several projects related to both Neurosciences and Immunology and at different stages of Discovery & Development. Moreover, he leads the PBPK platform set up in the Development Science department.

Dr Henri Caplain - Association Française de Pharmacologie Translationnelle - Le Club, France

Dr Henri Caplain, MD, MSc is a physician, senior adviser in clinical development strategy and drug risk management. He is President of the 'Association Française de Pharmacologie Translationnelle - Le Club Phase 1'. This association is a founding member of EUFEMED. After 15 years as primary investigator for early phase clinical trials and medical scientific director within a French CRO 'Aster-Group', he joined Sanofi-Synthelabo Research as head of clinical pharmacology and Exploratory, member of the R&D board. He became associate VP, deputy-head of worldwide clinical pharmacology, then head of the risk management center of excellence for Sanofi, member of the Benefit-Risk Assessment Committee chaired by the CMO.

Dr Ann Gils - Therapeutic Drug Monitoring (TDM), Belgium

Ann Gils graduated as a Pharmacist and obtained her PhD in Pharmaceutical Sciences at KU Leuven in 1997. Subsequently, she worked as a post-doctoral researcher and became a full professor at KU Leuven in 2015.

Currently she is the principal investigator of the Therapeutic Drug Monitoring (TDM) group of the Laboratory for Therapeutic and Diagnostic Antibodies, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Belgium.

She has participated in TDM studies in the field of gastroenterology, dermatology and rheumatology and has published more than 250 papers in the field of thrombosis and therapeutic drug monitoring of biologicals.

Dr Stephan Glund - Boehringer Ingelheim, Germany

Stephan Glund was trained as pharmacist at the Martin-Luther-University Halle-Wittenberg, Germany. He obtained his PhD from the Karolinska Institute in Stockholm in 2007, followed by a postdoctoral fellowship in CardioMetabolic Research at Boehringer Ingelheim, Biberach. In 2011 he moved to the Clinical PK/PD group within Boehringer Ingelheim, supporting clinical studies and development programs as pharmacokineticist. Additionally, he headed the Data Evaluation and Reporting Team (2013-2017) and currently leads a team of study and project pharmacokineticists within the same group.

Mr Roberto Gomeni – Pharmacometrica, France

Roberto Gomeni, PhD, obtained a degree in Mathematics from the University of Milano (Italy), a PhD in Pharmacokinetics and HDR from the University of Montpellier I (France). He was the former global head of Pharmacometrics at GlaxoSmithKline R&D, King of Prussia, PA (USA). He is the founder of Pharmacometrica, a global provider of consulting services in Pharmacometrics. He is, Adjunct Professor with the Division of Pharmacotherapy and Experimental Therapeutics in the UNC Eshelman School of Pharmacy at The University of North Carolina at Chapel Hill and is author of more than 170 original research papers published in international scientific journals.

Professor Dr Jan de Hoon - University of Leuven / University Hospitals Leuven, Belgium

After obtaining a Master's degree in Chemical Sciences Jan de Hoon was trained as a MD and specialised in General Internal Medicine at the University of Leuven. Subsequently, he became a certified Clinical Pharmacologist and obtained a PhD in Medical Sciences at the University Medical Centre of Maastricht in The Netherlands.

Jan has almost 25 years of experience in clinical pharmacology, partly in industry, partly in academia. He has a special interest in early clinical drug development including exploratory clinical trials, first-in-man, imaging and biomarker studies.

He is a board member – previous president – of EUFEMED: the European Federation for Exploratory Medicines Development which was founded in 2015. He is vice-president of the Belgian Association of Phase I Units (BAPU) of which he was also one of the founding members. At an international level he is member of the British Pharmacological Society, Council member for Belgium within the European Association for Clinical Pharmacology and Therapeutics (EACPT) and was a board member of the Dutch Society for Clinical Pharmacology and Biopharmacy.

At present, he is appointed as Full Professor in Pharmacology / Clinical Pharmacology at the Faculty of Medicine of the University of Leuven (KU Leuven). Since 2000 he is heading the Center for Clinical Pharmacology, an Academic Research Organisation located in the University Hospitals of Leuven near Brussels, with a focus on early clinical drug development.

Dr Lars Kuepfer - Bayer AG, Institute of Applied Microbiology of the RWTH Aachen, Germany

Lars Kuepfer is a senior scientist in the Systems Pharmacology group of Bayer AG in Leverkusen and at the Institute of Applied Microbiology of the RWTH Aachen. He studied chemical engineering at the TH Karlsruhe, RWTH Aachen and Carnegie Mellon University, Pittsburgh, and received his Ph.D. degree from ETH Zurich. In his current position, he works on pharmacokinetic and pharmacodynamic modeling of novel drug candidates thereby supporting decision making along the pharma development process. Lars Kuepfer's main research interests are in the areas of physiologically-based pharmacokinetic (PBPK) modelling, toxicology and quantitative systems pharmacology (QSP).

Dr Maxime Le Merdy - Simulations Plus, Switzerland

Before joining Simulations Plus as a Scientist II, Dr. Le Merdy received a Pharm.D. from University Paris-Descartes in 2015. In 2014, he received his master's degree in Pharmacometrics from the same university. He joined the FDA in 2017 as a Post-doctoral fellow in the Division of Quantitative Method and Modeling within the Office of Generic Drugs, where he developed his expertise in PBPK models for locally acting products. Prior to this experience, he published on Ethyl-glucuronide, a biomarker of alcohol consumption and on physiological modification that affects children's pharmacokinetics.

Dr Meagan O'Brien - Regeneron Pharmaceuticals, UK

Meagan O'Brien is a Director of Early Clinical Development and Clinical Experimental Sciences at Regeneron Pharmaceuticals. Dr. O'Brien received her medical degree from Harvard Medical School and completed medical residency and a fellowship in infectious diseases in New York City at Columbia Presbyterian and New York University Medical Schools. Dr. O'Brien's NIH-sponsored academic research focused on innate immune dysregulation by chronic viral infections and chronic inflammation in HIV infection. Dr. O'Brien joined Regeneron in 2017 to work in Early Clinical development, with a focus on allergy and immunology.

Dr Pauline Traynard - Lixoft, France

Dr Pauline Traynard joined Lixoft in 2017 as Applications Manager. She has a multidisciplinary background focusing on computational and systems biology. After a double engineering degree specializing in computational biology from Ecole Polytechnique and MINES ParisTech (Paris, France) obtained in 2012, she applied different mathematical formalisms to model biological rhythms as part of her PhD studies at INRIA and IBENS Paris, and prostate cancer as a postdoctoral fellow in Institut Curie.

Prof. Dr. med. Hildegard Sourgens – EUFEMED, Germany

Prof. Dr. med. Hildegard Sourgens is a board-certified Clinical Pharmacologist and board-certified Pharmacologist and Toxicologist. She was head of an industry-owned Research Institute for Clinical Pharmacology and head of Clinical Pharmacology of a German CRO. Hildegard Sourgens is a consultant for the pharmaceutical industry since 1996 and is involved in early drug development projects as well as international and national scientific advice and approval procedures.

From 2014-2016 she served as president of the AGAH; since July 2017 she is the president of EUFEMED.

For more detailed information please see: www.sourgens.de

Dr Andreas Kovar - Sanofi, Germany

Andreas Kovar, Ph.D., F.C.P., is currently Assoc. Vice President for Pharmacokinetics, Pharmacodynamics and Metabolism at Sanofi in Germany. After receiving his Ph.D. at the University of Tübingen, he held there a teaching position in Medicinal Chemistry. Subsequently, he did preclinical and clinical research on PK/PD correlations with a two-year scholarship of the DFG (German Research Foundation) at the University of Florida, Gainesville, USA. In 1997 he joined Merck KGaA where he held various positions in research and clinical drug development such as Global Head Clinical Pharmacology and Pharmacokinetics for Merck Serono, Geneva and Vice President for Global Exploratory Medicine Merck in Darmstadt. In 2014 he joined Sanofi-Aventis as Distinguished Advisor for Modeling and Simulation.

Andreas serves since 2018 as the President Elect of the AGAH. He is a Fellow of Clinical Pharmacology of the American College of Clinical Pharmacology, has published 38 peer reviewed papers, articles, and book chapters and presented 90 posters and presentations at scientific meetings and congresses.

Dr Kenichi Umehara - Roche, Switzerland

Kenichi obtained his PhD from the University of Toho (Japan), after working in Prof. Dr. Sugiyama's laboratory. In 2002, Kenichi joined Astellas Pharma, then in 2009, moved to Novartis (Switzerland) to undertake postdoctoral research for hepatic clearance prediction. Subsequently, he was appointed laboratory head for DDI assessment supporting global project teams. Kenichi also has experience in interactions with HA's that include PBPK modeling, to propose dose adjustment with concomitant medications resulting in waiver of clinical studies. In 2018 Kenichi joined the in vitro PK and DDI group in Roche Pharmaceutical Research and Early Development. He contributes to translation of the in vitro DDI results into models to understand the human situation.

PRE-CONFERENCE WORKSHOP SPEAKER ABSTRACTS

Wednesday 15 May

Workshop 1: Modelling and simulations, including PBPK to improve the clinical development

11.15 – 11.45

Principles of modeling and simulation including physiology-based pharmacokinetic (PBPK)
Mr François Bouzom - UCB Biopharm, Belgium

To succeed in curing a disease with any treatment, it is necessary to define the right drug at the right dose regimen for the right patient. In pharmaceutical companies, in Research and Development (R & D), the teams focus on these 3 R's to design the future drugs.

From the very early stages of the drug development process, it is important to combine the data and the understanding provided by different tools and experiments to perform a critical analysis of the available results and anticipate the future steps. To do so, it is key to have tools supporting the data analysis by combining them in a simpler way, ideally mechanistic: that is the purpose of any PharmacoKinetic (PK), PharmacoKinetic and PharmacoDynamic (PK/PD) or Physiologically Based PharmacoKinetic (PBPK) models. And once these models are available, they allow assumption testing by performing simulations to inform and design the future development stages.

The presentation is going to summarise the principles, the values and the limitations of different modelling approaches currently used for R & D in pharmaceutical sciences.

11.45 – 12.30

A general in-silico framework for maximizing the benefit-risk ratio of a treatment
Mr Roberto Gomeni – Pharmacometrica, France

The net benefit of a treatment (CB) is usually defined by the relationship between clinical improvement and risk of adverse events: the benefit-risk ratio. The convolution-based modeling approach has been proposed as a tool for optimizing the CB of a pharmacological treatment (1). The optimization of the benefit-risk ratio can be achieved by identifying the most adequate dose (and/or dosage regimen) jointly with the best performing in-vivo release properties of a drug. A general in-silico tool is presented for identifying the dose, the in-vitro and the in-vivo release properties that maximize the benefit-risk ratio using convolution-based modeling, exposure-response model, and surface response analysis. A case study is presented to illustrate how the benefit-risk ratio of methylphenidate for the treatment of Attention-Deficit/Hyperactivity Disorder can be maximized using the proposed strategy. The results of the analysis identified the characteristics of an optimized dose and in-vitro/in-vivo release suitable to provide a sustained clinical response with respect to the conventional dosage regimen and formulations.

Reference

[1] Gomeni R, Fang L, Bressolle-Gomeni F, Spencer TJ, Faraone SV, Babiskin A. A general framework for assessing IVIVC as a tool for maximizing the benefit-risk ratio of a treatment using a convolution-based modeling approach. *CPT Pharmacometrics Syst Pharmacol. 2019 Jan 18. doi: 10.1002/psp4.12378.*

13.15 – 13.45

Simulation of first-in-human using an allometrically scaled population mechanistic TMDD model
Dr Géraldine Ayral – Lixoft, France

While simple allometric scaling of clearance and volume is often sufficient for small molecules, the nonlinear PK of many biologics imposes the use of more advanced methods to predict the PK in human in order to determine the first in human dose from preclinical data. Model-based approaches integrating as much mechanistic information as possible from all phases have proven valuable. We give an illustration of how this can be done in practice with the MonolixSuite, using cynomolgus monkey data for the fully human IgG2 monoclonal antibody PF-03446962 targeting ALK1 [1]. First a TMDD population model was developed to characterize the nonlinear PK observed in the drug concentration profiles of 14 monkeys. To take all available information into account, in vitro and literature information on parameter values were used as priors. Then, to predict the human PK, physiological PK parameters were allometrically scaled while the mechanistic parameters were set to the human experimentally measured values. The impact of the scaling assumptions could be assessed using a sensitivity analysis. The comparison of the predictions with actual phase I patient data shows that predictions where within 1 to 2 fold of observations. This modeling and simulation workflow is especially easy and efficient to implement using the applications of the MonolixSuite.

Reference

[1] Luu, K. T., Bergqvist, S., Chen, E., Hu-Lowe, D., & Kraynov, E. (2012). A Model-Based Approach to Predicting the Human Pharmacokinetics of a Monoclonal Antibody Exhibiting Target-Mediated Drug Disposition. Journal of Pharmacology and Experimental Therapeutics, 341(3), 702–708.

13.45 – 14.15

From phase I data to phase II trial design: simulation and extension of a population pharmacokinetic model
Dr Pauline Traynard - Lixoft, France

Clinical trials required to demonstrate the efficacy of new drugs and regimens are often expensive and time consuming. The development of pharmacokinetic/pharmacodynamic models and their utilization with predictive tools can accelerate drug development by evaluating some arms or trials with in silico simulations.We show how modelling and subsequent simulations of a phase I dataset with PK measurements in 12 healthy patients of vanoxerine (GBR12909) [1], a dopamine reuptake inhibitor that has been researched for use in treating cocaine dependence, informs the design of phase II clinical trials. We use the user-friendly and integrated framework provided by the MonolixSuite to develop a complete model-based analysis workflow, including non-compartmental PK parameters computation, the building of a simple population model to characterize the variability observed in the drug concentration profiles, and simulations based on the estimated parameters.

The developed model first permits interpolation and assessment of relevant clinical endpoints while taking into account the inter-individual variability and estimation uncertainty. Then, extrapolation beyond the conditions of the phase I trial allows the selection of promising doses and trial designs, and offers putative predictions of effect response and new administration routes.

Reference

[1] Vocci FJ, Acri J, Elkashef A. Medication development for addictive disorders: the state of the science. Am J Psychiatry. 2005;162(8):1432–40

14.15 – 14.45

How PBPK modelling together with Bayesian statistics and targeted clinical data can be used to predict drug pharmacokinetics across patient populations?
Dr Lars Kuepfer - Bayer AG, Institute of Applied Microbiology of the RWTH Aachen, Germany

Translation of knowledge between different preclinical and clinical phases is a key challenge in pharmaceutical development programs. It is a plausible hope that computational modeling will overcome several of today's limitations in pharmaceutical research by supporting systematic concepts for processing, curation and re-evaluation of information and data. In particular, physiologically-based pharmacokinetic (PBPK) models represents a promising possibility since PBPK models allow the integration of experimental data from different layers of biological organization to mechanistically describe the of physiological processes underlying drug ADME. In my talk, I will give different examples how model-based approaches for clinical translation will help to translate preclinical findings from animal models to human healthy volunteers and to how to furthermore bridge between different patient subgroups. I will also outline how Bayesian approaches together with PBPK modelling allow to acquire the functional origins of inter-individual variability in the physiology of patient subgroups.

14.45 – 15.15

Various examples for the integration of cellular effect models from computational systems biology into whole-body PBPK models
Dr Lars Kuepfer - Bayer AG, Institute of Applied Microbiology of the RWTH Aachen, Germany

A thorough mechanistic understanding of physiological processes at different levels of biological organization is necessary to reliably simulate and predict pharmacological and toxicological effects of xenobiotics in living organisms. To this end, specific computational modelling approaches at the whole-body level as well as at the cellular scale are necessary to provide a structural framework for the integration, processing and analysis of experimental data.

At the organism level, physiologically-based pharmacokinetic (PBPK) models describe drug pharmacokinetics at a large level of physiological detail. In particular, the processes underlying drug absorption, distribution, metabolism and excretion, respectively, are explicitly represented in PBPK models which may be used to quantify on- and off-target tissue concentrations of drugs. At the cellular scale, different modelling concepts have emerged from the field of systems biology which allow a targeted analysis of cellular responses in the face of specific external stimuli and perturbations. These concepts which allow a detailed description of drug pharmacodynamics can be differentiated as follows: (1) Stoichiometric models of cellular metabolism, (2) graph representations of cellular networks or (3) dynamic models, respectively. In my talk I will give several examples for integrative multiscale PBPK/PD models and I will also give an outlook for their role in quantitative systems pharmacology in the future.

15.45 – 16.30

Population-based and physiology-based PK models for drug-drug interaction trials and trials waiver
Dr Kenichi Umehara - Roche, Switzerland

Physiology-based pharmacokinetic (PBPK) modeling has been increasingly utilized to answer clinically untested scenarios and has been accepted by health authorities. The established methodology can drive important benefit – risk decisions for drugs, representing various possibilities: a) The waiving of unnecessary clinical PK and DDI studies; b) dose adjustment with co-medications of interacting drugs; and c) informing clinical study designs. In this presentation, published case examples of the use of PBPK modeling in the PK and DDI evaluation will be shared. The case examples include DDI risk assessment for CYP enzymes, absorption DDI with proton pump inhibitors, and PK / DDI evaluation in special (sub)populations. As a future perspective, potential applications of PBPK modeling to drug development will be presented, in alignment with the guideline documents by FDA and EMA.

16.30 – 17.00

Advance current PBPK model applications to support internal development and regulatory decisions
Dr Maxime Le Merdy - Simulations Plus, Switzerland

The U.S. Food and Drug Administration (U.S. FDA) describes a Physiologically Based Pharmacokinetic (PBPK) analysis such as models and simulations that combine physiology, population, and drug characteristics to mechanistically describe the PK and/or pharmacodynamic (PD) behaviors of a drug. Throughout a drug's life cycle, PBPK model predictions can be used to support decisions on whether, when, and how to conduct certain clinical pharmacology studies, and to support dosing recommendations in product labeling (U.S. FDA, PBPK analysis, Guidance for industry). Simulations Plus collaborates with the U.S. FDA to both, develop new PBPK, and to advance current PBPK models uses to support drug's development and regulatory decisions.

17.00 – 18.00

How to obtain biowaivers for clinical trials using PBPK, two case studies
Dr Maxime Le Merdy - Simulations Plus, Switzerland

Presentation of two case studies:

Simulations Plus partnered with an actor of the pharmaceutical industry to construct a model using in vivo data collected from tablets manufactured with non-particle-engineered API. Using parameter sensitivity analysis and virtual bioequivalence trial simulations it was shown how the change in manufacturing process would not affect PK metrics. Ultimately, regulatory agencies approved the sponsor's biowaiver application.

Long acting injectables (LAI) generic products development is extremely limited due to the cost of the studies needed prior approval by the regulatory agencies. Simulations Plus and the U.S. FDA collaborate since 2015 to develop specific PBPK models for these drugs within the intramuscular dosage route model in GastroPlus©.

Wednesday 15 May

Workshop 2: Early clinical development of biologics – what is so different about it?

11.10 – 12.45

New therapeutic concepts
Dr Philip Barrington - Faculty of Pharmaceutical Medicine, UK

Dr Philip Barrington will discuss the development of Biological agents focusing mainly on monoclonal antibodies. The following topics will be discussed: The potential issues in developing antibodies with limited binding in animal species, Methods of prolonging the half-life of peptides, Check point agonists and antagonists, CAR-T cell therapy and alternative approaches, The use of antibodies as 'targeting' agents for cytotoxic chemicals and SiRNA, 'Multi functional' antibodies, Oral delivery of peptides/proteins and JAK inhibitors in autoimmune disease.

13.30 – 15.00

What is different in PK of biologicals
Dr Stephan Glund - Boehringer Ingelheim, Germany

Biologics are a fascinating class of therapeutics that provide new treatment options for many diseases, including some that had no small molecules-based therapy available. However, biologics are not simply large chemicals but convey additional levels of complexity. For example, posttranslational modifications, resulting from their production in living cells, can affect the pharmacokinetics and pharmacodynamics of these molecules.

The presentation will mainly focus on IgG antibodies and Fab-fragments. After a general introduction, the following topics will be touched: ADME characteristics with special attention to elimination processes, including target mediated drug disposition and the relevance of binding to the neonatal Fc-receptor (FcRn), Impact of anti-drug antibodies on PK and PD, Drug-drug interactions and Comparability.

15.15 – 16.45

How to approach PD and safety
Dr Meagan O'Brien - Regeneron Pharmaceuticals, UK

Biologics are therapeutic products that are produced from living organisms or contain components of living organisms, including monoclonal antibodies, recombinant proteins, tissues, genes, allergens, cells, blood components, blood, and vaccines. With a focus on monoclonal antibodies, we will discuss key concepts regarding safety and pharmacodynamics in the design and implementation of early clinical development studies.

16.45 – 17.45

ADAs / Immunogenicity
Dr Ann Gils - Therapeutic Drug Monitoring (TDM), Belgium

Chronic inflammatory diseases such as rheumatic diseases, spondyloarthritis, inflammatory bowel diseases and psoriasis have a high prevalence and typically start early in life, thereby strongly affecting the quality of life and productivity of young and active individuals. Patients have to be treated life-long and this requires safe, tolerable and cost-effective treatments. Since biologicals interact with a specific target, they are in general not toxic for the liver and kidney. However, biologicals have the potential to induce an immune response which can be determined by measuring anti-drug antibodies. The occurrence of immunogenicity is dependent on intrinsic factors such as protein structure, glycosylation and the covalent attachment of polyethylene glycol to the therapeutic protein and by extrinsic factors such as patient's genetics and co-medication as well as the route, dose and frequency of administration. The concentration of the drug and the effectiveness of the drug can be influenced by the incidence of anti-drug antibodies. The formation of anti-drug antibodies is influenced by numerous factors including co-medication. Assays to monitor drug concentrations and formation of antibodies will be discussed in this session.

PROGRAMME: THURSDAY 16 MAY 2019

08.00	**Registration**
08.45	**Welcome and Introduction** Hildegard Sourgens, Germany
SESSION 1: CURRENT AND FUTURE OPTIONS FOR VIRTUAL TRIALS IN EARLY MEDICINES DEVELOPMENT Chairs: Eric Legangneux, France and Georg Wensing, Germany	
09.00	Keynote lecture **The potential role of virtual trials in early medicines development: Beyond pharmacology to mechanisms** Adriano Henney, UK
09.20	**The in silico paradigm: understanding the potential of mechanistic models and their limitations, adapting organizations and building the necessary expertise** François-Henri Boissel, France
09.40	**The virtual physiological human – impact on early medicines development** Stig Omholt, Norway
10.00	**Open forum discussion** With session chairs, speakers, and Ingrid Klingmann, Belgium
10.45	Refreshments and Exhibition Viewing
SESSION 2: TRENDS AND INNOVATION Chairs: Henri Caplain, France and Yves Donazzolo, France	
11.15	**#WeAreNotWaiting for better diabetes care** Andrew Warrington, Switzerland
11.45	**Engineering allogeneic immune cells to generate off-the-shelf CAR T-cell immunotherapies** Roman Galetto, France
12.15	**Translation of gene therapeutics in neurological and neuromuscular diseases** Brian K. Kaspar, Switzerland
12.45	Lunch and Exhibition Viewing
SESSION 3: GUIDED POSTER TOURS AND SELECTED ORAL PRESENTATIONS Chairs: Sylvie Rottey, Belgium and Tim Hardman, UK Selection of posters: Sylvie Rottey (Chair), Jan de Hoon, Tim Hardman, Henri Caplain, George Wensig and Bob Wilffert	
13.45	**Guided poster tours**
14.15	**Oral presentations** (Five presentations selected from submitted abstracts) 3.1: **Diurnal and racial variance of white blood cell parameters in early phase clinical trials: a retrospective analysis of pooled data from multiple phase I trials** Simon Coates, UK
14.30	3.2: **Do we need pharmacokinetic data during each data review meeting in adaptive first-in-human trial? From guideline to practice** Nariné Baririan, Belgium
14.45	3.3: **Impact of cholinergic tone on the binding of PET tracer [11C]MK-6884, a positive allosteric modulator of M4 acetylcholine receptor in monkeys and healthy elderly volunteers** Inge De Lepeleire, Belgium
15.00	3.4: **Outcome of patients participating in early phase oncology trials at the Drug Research Unit Ghent (D.R.U.G.), Belgium** Brant Delafontaine, Belgium
15.15	3.5: **Volumetric Absorptive Microsampling (VAMS) for Blood Collection in Clinical Studies of Padsevonil** Hugues Chanteux, Belgium
15.30	Refreshments and Exhibition Viewing

PARALLEL BREAKOUT SESSIONS	
16.00-17.30	**1. Digital support to study performance in early phase development – from recruitment to remote data collection** Robert Rissmann, The Netherlands and Ingrid Klingmann, Belgium **Pasteur Auditorium**
	2. Lay summary requirements – consequences for Phase I trials Kerstin Breithaupt-Gröegler, Germany and Leonie Leithold, Germany **Commission Room Rhone 1**
	3. Transparency requirements for Phase I trials in times of transition Gerard Koëter and Sander van den Bogert, The Netherlands **Commission Room Rhone 2**
	4. What is acceptable/ethical to test in healthy subjects?Sylvie Rottey, Belgium and Jan de Hoon, Belgium **Commission Room Rhone 3A**
17.30	End of Day 1
19.30-22.30	**Conference Dinner** – Hèrmes River Boat

PROGRAMME: FRIDAY 17 MAY 2019

SESSION 4: UPDATE ON REGULATORY CONSIDERATIONS FOR EARLY CLINICAL DEVELOPMENT (INCLUDING BREXIT) Chairs: Mike Hammond, UK and Ingrid Klingmann, Belgium	
09.00	**MHRA perspective** Ian Rees, UK
09.20	**EMA perspective** Fergus Sweeney, The Netherlands
09.40	**Industry perspective** Nick Sykes, Pfizer, UK
10.00	Round table discussion
10.30	Refreshments and Exhibition Viewing
10.45-12.15	**Parallel break-out sessions** The same workshops as those presented on Thursday will be repeated and will be held in the same rooms
12.15	Lunch and Exhibition Viewing
SESSION 5: HOW TO BE PREPARED Chairs: Jörg Täubel, UK and Jan de Hoon, Belgium	
13.15	**Phase I trials in patients: new approaches and designs in Oncology** Nuria Kotecki, Belgium
13.45	**Challenges in exploratory clinical research** Maarten Van den Boer, Belgium
14.15	**Current perspectives on digital biomarker development in early clinical research** Virginia Parks, USA
14.45	**Closing remarks – How to be prepared!** Yves Donazzolo, France
15.00	End of Conference

SPEAKER BIOGRAPHIES

Mr François-Henri Boissel - Novadiscovery, France

François-Henri holds an MSc in Management from ESSEC Business School. Prior to founding NOVADISCOVERY, he spent 4 years with the investment bank Lehman Brothers in London and Tokyo where he has developed an expertise in financial engineering, deal structuring & execution. François-Henri has participated in securitization deals across a wide range of assets representing total completed financings in excess of US$ 500 million in Europe and Asia.

As Novadiscovery's cofounder and CEO since 2010, François-Henri has honed a variety of skills ranging from corporate structuring to business development and people management.

Dr Kerstin Breithaupt-Gröegler - KBR Clinical Pharmacology Services, Germany

Dr Kerstin Breithaupt-Grögler (MD) studied medicine at J.W. Goethe-University Frankfurt, Germany (1976-1983). After state approval as physician and medical thesis (doctor of medicine, summa cum laude) worked as Junior Research Fellow at Center of Physiology, University Frankfurt (1983-1985).

From 1986 to 1995 Research Physician / Clinical Investigator at Center of Cardiovascular Pharmacology, Mainz-Wiesbaden, Germany and Board Certification in Clinical Pharmacology. Since 1995 working as independent consultant in clinical pharmacology and medical writer. More than 20 years experience in planning, conduct, evaluation and reporting of Phase I to III clinical trials, writing of expert reports including safety dossiers, clinical summaries / overviews, scientific presentation and publication (30 original papers, more than 80 abstracts and oral presentations).

Founding member of the German Association of Applied Human Pharmacology (AGAH e.V., Hamburg), Board Member since 1997; President 2012-2014, Past President 2014-2018, since 2018 Consultant to the AGAH Board. AGAH Delegate to EUFEMED (European Federation for Exploratory Medicines Development, Brussels). Member of scientific programme committees, conduct of workshops and conferences, training courses in exploratory medicines development, qualification of study teams.

Dr Henri Caplain - Association Française de Pharmacologie Translationnelle - Le Club, France

Dr Henri Caplain, MD, MSc is a physician, senior adviser in clinical development strategy and drug risk management. He is President of the 'Association Française de Pharmacologie Translationnelle - Le Club Phase 1'. This association is a founding member of EUFEMED. After 15 years as primary investigator for early phase clinical trials and medical scientific director within a French CRO 'Aster-Group', he joined Sanofi-Synthelabo Research as head of clinical pharmacology and Exploratory, member of the R&D board. He became associate VP, deputy-head of worldwide clinical pharmacology, then head of the risk management center of excellence for Sanofi, member of the Benefit-Risk Assessment Committee chaired by the CMO.

Professor Dr Jan de Hoon - University of Leuven / University Hospitals Leuven, Belgium

After obtaining a Master's degree in Chemical Sciences Jan de Hoon was trained as a MD and specialised in General Internal Medicine at the University of Leuven. Subsequently, he became a certified Clinical Pharmacologist and obtained a PhD in Medical Sciences at the University Medical Centre of Maastricht in The Netherlands.

Jan has almost 25 years of experience in clinical pharmacology, partly in industry, partly in academia. He has a special interest in early clinical drug development including exploratory clinical trials, first-in-man, imaging and biomarker studies.

He is a board member – previous president – of EUFEMED: the European Federation for Exploratory Medicines Development which was founded in 2015. He is vice-president of the Belgian Association of Phase I Units (BAPU) of which he was also one of the founding members. At an international level he is member of the British Pharmacological Society, Council member for Belgium within the European Association for Clinical Pharmacology and Therapeutics (EACPT) and was a board member of the Dutch Society for Clinical Pharmacology and Biopharmacy.

At present, he is appointed as Full Professor in Pharmacology / Clinical Pharmacology at the Faculty of Medicine of the University of Leuven (KU Leuven). Since 2000 he is heading the Center for Clinical Pharmacology, an Academic Research Organisation located in the University Hospitals of Leuven near Brussels, with a focus on early clinical drug development.

Dr Yves Donazzolo – Eurofins Optimed, France

Dr Yves Donazzolo is a medical doctor and a clinical pharmacologist. In 1990, he cofounded Eurofins Optimed, a company dedicated to the early clinical development of drugs and health products in Europe with particular expertise in early development studies, from First-into-Human to Proof-of-Concept trials. He has served as Principal Investigator in several hundreds of trials. He is an active member of the French Club Phase I society, where he has served as President for two terms. More recently he has been a founding member of EUFEMED, the newly formed European Federation for Exploratory Medicines Development. In addition, he is a member of SFP, ASCPT, BPS and ACCP. He has been a lecturer in several teaching programs in clinical pharmacology and drug development and is responsible for a Master Module at Grenoble Alps University.

Dr Roman Galetto - Cellectis SA, France

Bachelor degree in Biological Sciences & Clinical Biochemistry from the Catholic University of Cordoba (Argentina, 1996). Started research at the Center for the Study of Inherited Metabolic Diseases (Argentina), and obtained his PhD in Molecular Biology at the University of Cantabria, (Spain, 2001), followed by a post-doc at the Pasteur Institute in Paris.

Joined CELLECTIS in 2007, working on the use of nucleases for therapeutic applications prior to working on UCART Development. He was in charge of the UCART & Process Development Group, participating in the development of UCART product candidates from screening to lead selection and validation in vitro and in vivo, and in the development of GMP compatible large-scale manufacturing process. Currently involved in UCART Preclinical Development and in defining and completing non-clinical data packages for regulatory submissions. Familiar with all the stages of development of UCART products, through interactions with CMC, manufacturing, translational, clinical and regulatory teams.

Dr Mike Hammond - AHPPI / Clinical Management Solutions Ltd, UK

After completing a Graduate and Post-Graduate training in Experimental Pharmacology, Mike joined Bayer UK as a team leader in drug discovery for their Anti-inflammatory Anti-Asthma programme.

Although not specifically GCP there were several opportunities to cooperate with clinical groups in UC London and INSERM58 Montpellier using clinical subjects, sharing some of their assay resources. During this time, they experienced the early stages of experimental studies in man, the former lung lavage mediator release and the latter allergen challenge and cortisol profiling. The results validated observations that we had made in their laboratory models.

In 1990 the opportunity arose to transfer to the Clinical Research & Development department to implement the Clinical Trial quality management system Good Clinical Practice to clinical R&D. Mike became part of the Global Quality Management Group which included GLP, GMP, Pharmacovigilance and Biometrics. Training and audits were required globally including offices in USA, Japan, Europe and South Africa. In addition, audit visits were made to investigational and vendor sites.

After seven years Mike had the necessary knowledge and experience to go freelance and set up his own company. Mike continued to perform work for Bayer.

Mike was fortunate to be offered a Senior Director Quality Management position with one of his Japanese clients. The small size of this company gave him the opportunity to get closer to the treatment of rare and complex diseases. It also extended his experience to First in Human trials. This continued until the company reorganised on 2013, when he returned to his freelance work.

Dr Tim Hardman - Niche Science & Technology Ltd, UK

Dr Tim Hardman, Managing Director of Niche Science & Technology Ltd., has over 25 years of experience in the bioscience research sector, working across academia and industry and playing a key role in many innovative collaborations and partnerships. Tim gained his PhD at Imperial College London. Following 15 years of post-doctoral research in the fields of metabolic disease, diabetes, dyslipidaemia and hypertension; Dr Hardman spent several years in the medical education sector, establishing his company in 1998. Niche Science & Technology Ltd. is a specialist CRO focused on Regulatory Affairs, Medical Writing and Clinical Project Management services to the pharmaceutical industry and academia.

Dr Adriano Henney - The Avicenna Alliance for Predictive Medicine, UK

Dr Henney has a PhD in Medicine and a research background in cardiovascular disease at the pathological, cellular, molecular and genetic level. After an academic career in laboratories in London, Cambridge and Oxford, he moved into industry spending 13 years with AstraZeneca. Ultimately leading global programmes exploring strategic improvements aimed at reducing drug

failure in development, he created and headed a new department that focused on pathway mapping and modelling, which evolved to establish the practice of Systems Biology, supporting projects in discovery and development. Dr Henney has extensive experience in directing and managing large, complex teams across disciplinary, cultural and geographic boundaries, latterly in the area of Systems Biology and Systems Medicine. His experience in this area led to an invitation to direct the major €50M German national flagship programme, The Virtual Liver Network, at the time the largest Systems Biology programme in Europe, managing over 200 contributing scientists from a range of disciplines, including clinicians, in 36 independent institutions, including industry. Following the end of the programme, Dr Henney was elected to be part-time Executive Director of the Virtual Physiological Human Institute, a not-for-profit organisation promoting the use of computational modelling and simulation to interpret quantitative biological information and understand the dynamics of biological and physiological function. As part of that role, he was responsible for establishing a new partnership with industry, The Avicenna Alliance for Predictive Medicine, a not-for-profit organisation that focuses on developing a policy framework supporting the use of in silico technologies in medicine, and of which he is now Chairman of the Board of Directors.

Dr Brian K. Kaspar - AveXis, Inc, Switzerland

Dr Kaspar is Scientific Founder and Chief Scientific Officer at AveXis, Inc., a clinical-stage gene therapy company focused on the treatment of neurological diseases. He is a former Endowed Chair and Professor of Pediatrics at The Ohio State University and principal investigator at Nationwide Children's Hospital. His work on gene therapy for spinal muscular atrophy was Science's People's Choice Award for 2017 Breakthrough of the Year. Dr. Kaspar. He is a Fellow of the American Association for the Advancement of Science (FAAAS) with over 100 peer reviewed manuscripts and book chapters. He serves on NIH Review Panels, a number of ASGCT committees, as well as serves on the editorial board of Molecular Therapy.

Dr Ingrid Klingmann - PHARMAPLEX bvba, Belgium

Physician, specialized in General Medicine, Clinical Pharmacology and Pharmaceutical Medicine with over 30 years of experience in different senior medical, operational and managerial functions in pharmaceutical industry, CROs and clinical trial sites with focus on clinical trial design and management, ethical and regulatory aspects. Since January 2003 she has her own pharmaceutical development and site management support consulting company. Dr Klingmann is Chairman of the Board of the European Forum for Good Clinical Practice (EFGCP) and President of PharmaTrain. She is a Regent in AGAH and an AGAH Delegate in the EUFEMED Board.

Prof. Dr. Gerard Koëter - UMCG, Netherlands

Gerard Koëter studied medicine at the University of Groningen, The Netherlands and graduated in 1974. Next, he was trained as lung physcian at the University Hospital in Groningen and was certified as such in 1979. In 1984 he completed his Ph.D training. Thereafter, he spent an eight months training period at the McMaster University in Hamilton, Canada. In 1988 he was appointed as Professor in Lung Diseases and Tuberculosis at the University of Groningen and became head of the department of Lung Diseases at the University Hospital (UMCG). He was responsible for patient care, clinical research, and training of medical students.

He (co-)author of more than 250 peer reviewed scientific publications. Between 2006 and 2008 he worked in the health care of Groningen in the treatment of patients with tuberculosis. In 1984 he was one of the founders of the research ethics committee in Assen. Between 2008 and 2014 he was chairman of the Central Committee of Medical Ethics in The Hague.

Dr Nuria Kotecki - Jules Bordet Institute, Belgium

Nuria Kotecki is a medical oncologist graduated from Lille 2 University of Health and Law in 2014 and currently working at Jules Bordet Institute, in Brussels. During her internship, she has been trained in the clinical development of new cancer drugs at Jules Bordet Institute. Her main fields of activity and research interests are breast cancer and development of innovative medical therapeutics for solid tumor patients. She has participated in several clinical trials from phase I to later phases. Dr Nuria Kotecki is a member of different scientific organisations including ASCO and ESMO. She has authored and co-authored articles in national and international papers as well as many abstracts in congress.

Dr Eric Legangneux - Novartis Institute of Biomedical Research, France

Medical Doctor and Clinical Pharmacologist with twenty five years of international experience in the Pharmaceutical Industry and four years as Investigator in an academic environment. Currently leading the group of Clinical Pharmacology for Neuroscience at the Novartis Institute of Biomedical Research. Experienced in the clinical drug development from pre-clinical up to registration and beyond. Contributor to 10+ submissions and registrations of worldwide new drug applications. Translational medicine expert in neuro-psychopharmacology and sleep.

Dr Leonie Leithold - Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Leonie Leithold was trained as a medical biologist at the Radboud University Nijmegen and moved on to study neuroscience at the University of Edinburgh. She obtained her PhD in Biology from the Heinrich-Heine-Universität Düsseldorf. She joined Boehringer Ingelheim Pharma as a Regulatory Medical Writer in 2016. In her role, she writes regulatory documents such as clinical study reports for different indications and phases and clinical submission documents. In addition, she oversees the writing of lay summaries of clinical study results as lay summary expert and the part of a team developing lay titles for clinical studies.

Professor Stig Omholt - Norwegian University of Science and Technology (NTNU), Norway

Stig W. Omholt is director of the cross-campus biotechnology programme at the Norwegian University of Science and Technology (NTNU): NTNU Biotechnology: the Confluence of Life Sciences, Mathematical Sciences and Engineering. He is also research professor at the Faculty of Medicine and Health at NTNU. He has a broad scientific background in genomics, genetics, systems theory, computational physiology, ageing biology and evolutionary biology. He is board member of the "Virtual Physiological Human Institute", and the academia-industry coalition "Avicenna Alliance - Association for Predictive Medicine". With regard to medicine development he is occupied with how multiscale computational physiology and control theory can inform the identification of new drug targets and predict the high-level phenotypic effects from manipulating these targets.

Ms Virginia Parks - Takeda, USA

Virginia Parks has over 20 years of global drug development experience across multiple therapeutic areas including neuroscience, cardiovascular, metabolic disorders, and rare diseases. She is currently a Clinical Pharmacology Lead at Takeda (formerly Shire) in Boston. In this role, she was a key member of a project team for an early phase asset in neuroscience working on an initiative to develop a digital biomarker strategy. This included identification of wearable technology, analytics development and validation, patient engagement, and use of external data sources. Prior to joining Shire, Virginia worked for Pfizer and Wyeth where she was primarily focused on leading early stage exploratory programs. She received her master's degree in neuroscience from Kings College London, UK.

Mr Ian Rees - MHRA, UK

Ian joined the MHRA as a GMP inspector in 2001, prior to this Ian was a GMP inspector with the Veterinary Medicines Directorate for 2 years and before this worked for a start up biopharmaceutical firm for 14 years. In 2004, Ian became an Operations Manager responsible for the team of GMP inspectors based in London and was promoted to Expert GMP Inspector in 2006. Between 2008 and 2015, Ian was the MHRA representative on the EMA's GMDP Inspectors Working Group which has as its key responsibility the development and maintenance of EU GMP and GDP.

In August 2014 Ian became the Unit Manager Inspectorate Strategy and Innovation where he manages a team of Expert Inspectors and leads the development of the Inspectorate strategy across all GXP disciplines. Ian has been part of the MHRA team behind the Innovation Office and the UK cross regulatory Regulatory Advice Service for Regenerative Medicines (the 'One Stop Shop') which include HTA, HRA, HFEA, DEFRA, HSE, NICE and MHRA. These provide advice and guidance to individuals and organisations developing innovative medicines, medical devices or using novel manufacturing processes.

Mr Robert Rissmann - Leiden University Medical Centre, Netherlands

Robert Rissmann (1977) studied pharmacy at the Free University of Berlin, Germany. He obtained the licensure as pharmacist in 2004 and started subsequently a PhD project in Drug Delivery at the Leiden/Amsterdam Center for Drug Research (LACDR), Leiden University in the field of translational dermatology. In 2009 Robert successfully defended his PhD thesis in skin pharmacology. From 2010 until 2017 he was Director of Education at CHDR with main emphasis on clinical pharmacology and pharmacotherapeutics. With regard to research his key interests are translational models in both immunology and dermatology for drug development in early phase clinical research. He is board member of the Dutch Society of Clinical Pharmacology and Biopharmacy and board member of the Education committee of the British Pharmacological Society. In 2015 he was appointed Associate Professor at Leiden University Medical Centre. He has published over 40 manuscripts in peer-reviewed journals and is actively involved in the supervision and training of PhD students. Since 2017 he holds the position of Research Director Dermatology and heads the research group Skin Pharmacology and applies routinely trial@home applications.

Prof. Dr. Sylvie Rottey - Drug Research Unit Ghent (D.R.U.G.), Belgium

Sylvie Rottey studied Medicines at the Ghent University Belgium and a member of the staff at the department of Medical Oncology from October 2003. Specialized in uro-oncology and head and neck cancer, she is principle investigator of numerous phase II and III trials covering this topic since more than 10 years. Next to Medical Oncologist, she is Professor in Pharmacology, certified as Clinical Pharmacologist in 2008 (Dutch Society for Clinical Pharmacology & Biopharmacy). At the Ghent University she teaches clinical pharamcology (interactive tutorials) and gives courses clinical trials. From 2015 on, she heads the Drug Research Unit Ghent (D.R.U.G.) where first in human (healthy volunteer) trials and Oncology Phase I trials are executed.

She publishes in national and international peer reviewed journals and is speaker on national and international symposia. She is member of NVKFB (Dutch Society for Clinical Pharmacology & Biopharmacy), president of BAPU (Belgian Association of Phase I Units), vice president of BSMO (Belgian Society of Medical Oncology), president of BMUC (Belgian Mutidisciplinary Meeting on Urological Cancers), member of ESMO (European Society of Medical Oncology), member of ASCO (American Association of Clinical Oncology), member of the board of VWHHT (Flemisch Working Group on head and neck cancers), member of EORTC (European Organisation of Research and Treatment in Cancer).

Prof. Dr. med. Hildegard Sourgens – EUFEMED, Germany

Prof. Dr. med. Hildegard Sourgens is a board-certified Clinical Pharmacologist and board-certified Pharmacologist and Toxicologist. She was head of an industry-owned Research Institute for Clinical Pharmacology and head of Clinical Pharmacology of a German CRO. Hildegard Sourgens is a consultant for the pharmaceutical industry since 1996 and is involved in early drug development projects as well as international and national scientific advice and approval procedures.

From 2014-2016 she served as president of the AGAH; since July 2017 she is the president of EUFEMED.

For more detailed information please see: www.sourgens.de

Mr Fergus Sweeney - European Medicines Agency, Netherlands

Fergus Sweeney is Head of Inspections, Human Medicines Pharmacovigilance and Committees Division at the European Medicines Agency. The Division provides the organisational and operational support to the Agency's Human Scientific Committees in close collaboration with the elected chairs and nominated members. It is responsible for pharmacovigilance and epidemiology, including signal detection and management, monitoring of products on the market and providing leadership for the Agency's pharmacovigilance system. It ensures the coordination of inspections and good practice standards, coordinates incident management in the area of safety and quality of human medicines in liaison with the European medicines regulatory network and maintains close contact with international partners in the areas of inspection and pharmacovigilance in conjunction with the Agency's International Affairs function. The Division oversees the work of the EU NTC Training platform, whose mission is to ensure good scientific and regulatory practice is spread across the European medicines regulatory network.

Fergus joined the Agency in 1999 in the Inspection Sector and was appointed Head of Sector, Compliance and Inspections in May 2009. In August 2013 he was appointed Head of Division Inspections and Human Medicines Pharmacovigilance which became the Inspections, Human Medicines Pharmacovigilance and Committees Division in 2016. Fergus has a Degree in Physiology (Trinity College Dublin, Ireland, 1979), a Doctorat de Troisiéme Cycle in cancer biology (Université de Paris, 1982), and a PhD in Pharmacology (UCD, Ireland, 1986). Prior to joining the Agency he worked in industry from 1982 to 1999, covering phase I-IV clinical research, pharmacovigilance and laboratory activities, primarily in the field of quality assurance.

Mr Nick Sykes – Pfizer, UK

Nick Sykes has worked in Regulatory Affairs since 1992 at various companies and joined Pfizer's regulatory affairs team in 1998. His current role is heading a small team focussed on European and International regulatory policy. Over the years Nick has also had interim roles working on projects or leading teams of regulatory strategists in Pfizer's European regulatory strategy group.

Externally, Nick is a member of a number of industry trade association committees (including the EFPIA Regulatory Strategy Committee and as chair of the EFPIA Clinical Trials & Transparency Priority Working Group for the past four years). Nick is also an active member of DIA and TOPRA regularly presenting and chairing sessions at their meetings. During 2019 Nick is TOPRA President and is the Chair of the TOPRA Board.

Prior to joining Pfizer, Nick worked for SmithKline Beecham Pharmaceuticals, Cambridge Antibody Technology and PJB Publications. Nick earned a Bachelor's degree in Genetics/Microbiology from the University of Leeds in the UK and a Masters degree in Information Science from the University of Sheffield in the UK.

Dr Jörg Täubel - Richmond Pharmacology, UK

Dr Jörg Täubel is a medical practitioner and CEO of Richmond Pharmacology which he co-founded in 2001. He has worked in clinical pharmacology for 24 years and during that time he has conducted more than 400 early phase studies in patients and healthy volunteers; usually in the capacity of Principal Investigator since 1995. His experience ranges from first time in man (FTIM) to proof of concept (POC) studies. He has extensive experience in cardiology, neurology, gastroenterology, ethnic bridging studies.

His work currently focusses on providing expert advice in cardiac safety assessments and ethnic comparison studies. Dr Täubel is an honorary fellow at St George's University and author of over 50 publications in scientific journals. He is currently researching the role of hyperglycaemia in relation to sudden cardiac death in Type I diabetic patients. He presented his research at numerous international meetings and workshops in Europe, US and Japan.

Dr Maarten Van den Boer - Janssen Pharmaceutica, Belgium

Maarten Van den Boer Received his medical degree at the University of Antwerp in 2005, followed by his doctor's degree in internal medicine in 2012. In 2013 he joined Janssen Pharmaceutica as a Research Physician at the Clinical Pharmacology Unit. Since 2017 he is involved in early phase patient trials in the role as Exploratory Patient Study Clinical Leader.

Dr Sander van den Bogert - Apotheek Boekel, Netherlands

Sander van den Bogert completed pharmacy school in 2013. For his master's thesis, he conducted clinical epidemiology research under the supervision of Professor Kenneth Saag at the Center for Education and Research on Therapeutics on Musculoskeletal Disorders at Birmingham (U.S.A.). He also interned at the World Health Organization headquarters in Geneva (Switzerland) as member of a collaboration between WHO, the International Pharmaceutical Federation and the Dutch Ministry of Health, Welfare and Sports.

In 2013, Sander started a PhD track at the Utrecht Institute for Pharmaceutical Sciences (UIPS), division of Pharmacoepidemiology and Clinical Pharmacology. Between 2013 and 2017 he conducted research at the National Institute of Public Health and the Environment (RIVM), the Central Committee on Research Involving Human Subjects (CCMO) and the Medicines Evaluation Board (CBG-MEB), resulting in a doctoral thesis entitled "Trials & Tribulations. Studies on the fate, transparency and efficiency of clinical drug trials". As of September 2017, Sander started working as pharmacist at Apotheek Boekel in Boekel, the Netherlands. He is member of the Editorial Board of the Dutch Drug Bulletin.

Mr Andrew Warrington, Switzerland

Andrew Warrington is a patient, health hacker, and member of the #WeAreNotWaiting open source diabetes care movement. He is a contributor to the AndroidAPS artificial pancreas system. In his day job, he works in the pharma industry.

Prof. Dr. med. Georg Wensing - Bayer, Germany

Dr Wensing is Vice-President and Head of Clinical Pharmacology Cardiovascular/ Hematology at Bayer in Wuppertal, Germany. Georg Wensing is an MD by training and is board certified as internist and clinical pharmacologist. He received his medical training at the universities of Essen, Kiel and Erlangen-Nürnberg in Germany and in the Division of Clinical Pharmacology at Vanderbilt University in Nashville, TN. After joining Clinical Pharmacology at Bayer in 1992 he became subsequently Head of Pharmacodynamics at Bayer and Vice-President and Head Clinical Pharmacodynamics at Bayer Schering Pharma. In 2003, he received the venia legendi (Habilitation) for Internal Medicine/Clinical Pharmacology at the University of Essen, Germany, and in 2010, he was awarded the designation apl. Professor. Georg Wensing served for 6 years as Member of the Board of the “Deutsche Gesellschaft für Klinische Pharmakologie und Therapie (DGKliPha) “. Since 2009 he is Member of the Extended Board (Regent) of the „Arbeitsgemeinschaft für angewandte Humanpharmakologie (AGAH) “and in 2016 was voted AGAH President Elect. Since 2017 he is representing member of the AGAH in the “Verbund für Klinische Pharmakologie In Deutschland (VKliPha)” and since 2018 president of the AGAH.

SPEAKER ABSTRACTS

Thursday 16 May

Session 1: Current and future options for virtual trials in early medicines development

09.00 – 09.20

The potential role of virtual trials in early medicines development: Beyond pharmacology to mechanisms
Dr Adriano Henney, UK

The success rate of delivering novel medicines to market has continued to decline over the last 20 years despite the promises that genomic medicine would result in "a complete transformation in therapeutic medicine". The reliance on reductionist, cell and molecular screens that capitalise on detailed target information emerging from advances in molecular and cellular biology are likely to be part of the reason for this lack of success, as this approach lacks an understanding of the dynamics of the physiological networks that underpin these diseases. During the same period, there has been a growing belief

that integrative systems approaches involving computational modelling and simulation can help to unravel these complex systems, although adoption and reduction to practice of these approaches has been slow. "Virtual trials" run in computer models of human physiological systems have been successful in the development and testing of medical devices, but application within the pharma sector has been slower. Recently the emergence of Model Informed Drug Discovery and Development (MID3) has demonstrated that computational models are useful in refining classical pharmacometric studies, and also now to help understand toxicological mechanisms. Whilst this is encouraging, the need remains for in silico technologies to help improve our understanding of the pathogenetic mechanisms underpinning complex diseases.

09.20 – 09.40

The in silico paradigm: understanding the potential of mechanistic models and their limitations, adapting organizations and building the necessary expertise
Mr François-Henri Boissel, France

In silico clinical trials are emerging fast as a powerful addition to the drug development toolbox. The systematic use of mechanistic models to explore a large continuum of therapeutic hypotheses before being tested on humans is expected to de-risk early-stage clinical development and ultimately accelerate time to patient.

Understanding how to use theses models and what to expect from them is critical to their widespread adoption. Regulatory agencies are currently working on establishing a framework to include modeling and simulation in their workflows.

To be successful in this dawning age of digital evidence, pharmaceutical firms will need to adapt to this new paradigm by establishing functional teams assembling the necessary skillset.

09.40 – 10.00

The virtual physiological human – impact on early medicines development
Professor Stig Omholt - Norwegian University of Science and Technology (NTNU), Norway

Even though model-based drug development is gaining acceptance as a vital approach in understanding patient risk/benefit and attrition, a major characteristic of current drug targeting research is that one employs high-throughput screening of quite simple assays to identify a key molecule involved in a particular metabolic or signalling pathway specific to a disease condition or pathology that may be used to cure the patient by inhibiting or enhancing particular pathways or processes. This paradigm has also been one of the major drivers behind the development of genomics and the pursuit of large genome-wide association studies because it was thought that such studies would provide a plethora of putative drug targets for complex diseases. Considering the practical outcomes relative to the enormous resources that have been invested in these approaches, it is arguably need for trying out radically new drug targeting approaches that might enable us to both identify a plethora of new drug targets and dramatically reduce the high attrition rates we are currently observe.

Advanced computational physiology representations embedded in a control-theoretic framework of what causes and maintains complex disease states may provide the basis of such a new drug targeting paradigm. It allows us to invert the current bottom up approach and start from the disease phenotype and work our way down in a causally cohesive way to the molecular realm where we can link with drug design. The talk will outline the possibilities and challenges associated with this approach.

Session 2: Trends and innovation

11.15 – 11.45

#WeAreNotWaiting for better diabetes care
Mr Andrew Warrington, Switzerland

For 50 years the concept of an artificial pancreas was the subject of research and development, but no products were making their way to the market. When the technology to make such a device became widely available and affordable, a loose affiliation of patients, who could not wait any longer, took it upon themselves to build their own devices and prove they are safe and effective.

11.45 – 12.15

Engineering allogeneic immune cells to generate off-the-shelf CAR T-cell immunotherapies
Dr Roman Galetto - Cellectis SA, France

Chimeric Antigen Receptors (CARs) are engineered molecules that, when present at the surface of T-cells, enable them to recognize specific proteins or antigens that are present on the surface of target cells. These receptors provide then T-cells with a specific targeting mechanism to seek, identify, interact with and destroy the tumor cells bearing a selected antigen associated with that tumor.

CARs are today one of the most promising approaches to fight cancer, and have shown long-term durable remissions and remarkable objective response rates in patients with refractory leukemia. Most CAR T-cell therapy products are currently generated from autologous cells, with the limitation that they have to be manufactured in a “per patient” basis, which remains difficult to implement for lymphopenic and critically ill patients.

Cellectis has developed a standardized platform for manufacturing CAR T-cells from healthy donors to generate allogeneic “off-the-shelf” engineered CAR T-cell–based frozen products. This allogenic platform utilizes Transcription Activator-Like Effector Nuclease (TALEN®) gene editing technology to inactivate the TCRα constant (TRAC) gene, eliminating the potential for T-cells bearing alloreactive TCR’s to mediate Graft versus Host Disease (GvHD).

Production of these gene-edited CAR T-cells, named UCARTs (Universal Chimeric Antigen Receptor T-cells), can be industrialized and thereby standardized with consistent pharmaceutical release criteria, over time and from batch to batch. UCARTs represent indeed a paradigm shift in terms of ease of use, availability and the drug pricing challenge.

The presentation will cover key aspects of UCART technology, and highlight the main results of non-clinical studies performed to validate these product candidates.

12.15 – 12.45

Translation of gene therapeutics in neurological and neuromuscular diseases
Brian Kaspar[1]
Petra Kaufmann[1], Kevin Foust[1], Allan Kaspar[1], Jerry Mendell[2–4]

[1]AveXis, Inc., Bannockburn, IL, USA; [2]Center for Gene Therapy, Nationwide Children’s Hospital, Columbus, OH, USA; [3]Department of Pediatrics, Ohio State University, Columbus, OH, USA; [4]Department of Neurology, Ohio State University, Columbus, OH, USA

The discovery of gene therapeutics crossing the blood brain barrier opened the possibility to less invasively deliver gene therapeutics to the brain and spinal cord in an efficient manner. AAV serotype 9 delivered one-time by systemic or cerebrospinal fluid opened the possibility of treating neurological disorders. Over the past decade, multiple non-clinical studies have been performed showing the potential of this therapy to treat severe, life threatening neurological conditions. In this presentation, we will present the history and development of AAV9 to be utilized for the treatment of spinal muscular atrophy(SMA) as well as other neurological disorders. Further, we will highlight the challenges and overcoming’s to develop a drug for potential global approval.

Onasemnogene abeparvovec (AVXS-101) is an investigational, one-time GRT that treats the genetic root cause of SMA, a progressive neurological disease. AVXS-101 delivers the survival motor neuron gene (SMN) via a self-complementary adeno-associated serotype 9 viral vector (scAAV9) that crosses the blood-brain barrier. AVXS-101 is designed for immediate and sustained expression of SMN protein in non-dividing neurons, allowing for rapid onset and durable therapeutic effect.

In SMA mice, scAAV9-SMN improved survival (>200 versus 15 days in controls), and increased motor function (90% had righting ability at P13 versus ~20% in controls). In NHPs, scAAV9-GFP efficiently targeted motor neurons throughout the CNS. In the phase 1 trial, all patients survived, event free, at 24 months. In the therapeutic dose cohort, 11/12 patients reached CHOP-INTEND ≥40; 11 sat unassisted ≥5s, 10 for ≥10s, 9 for ≥30s. Two patients crawled, stood, and walked. In the long-term follow-up study (LTFU), 2 more patients sat ≥30s and 2 stood with support. No patient received nusinersen during the 24-month study period. Four patients had an asymptomatic transient rise in serum aminotransferase. The oldest patient is 59.2 months of age with 53.3 months of follow-up post–AVXS-101 therapy (as of September 27, 2018).

Significant development of this product including manufacturing and analytical development will be highlighted. To date, regulatory submissions for approval of onasemnogene abeparvovec have been submitted in the U.S., Europe, and Japan.

Session 3: Guided poster tours and selected oral presentations

For poster list see page 43-44.

14.15 – 14.25

3.1 Diurnal and ethnic variance of white blood cell parameters in early phase clinical trials: a retrospective analysis of pooled data from multiple phase I trials.

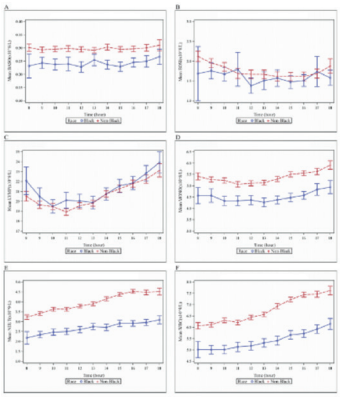
Simon Coates[1],
Sara Fernandes[1], Duolao Wang[2], Clare Umukoro[1], Dilshat Djumanov[1], Ulrike Lorch[1], Jörg Täubel[1 3].
[1]Richmond Pharmacology, St George's, University of London, UK
[2]Department of Clinical Sciences, Liverpool School of Tropical Medicine, UK
[3]St George's, University of London, UK

BACKGROUND: Circulating white blood cell count is a common inclusion criterion for clinical studies. We aimed to characterise the variance in circulating white blood cell (WBC) levels when categorised by time of day and self-ascribed racial group in early phase clinical trials and to assess the impact in participation rates.

METHODS: Data on WBC parameters were obtained retrospectively from 35 completed phase I clinical trials. Subjects were identified as either Black or Non-black and samples were grouped by time-of-day of phlebotomy (8:00 to 18:00). Data obtained from 73,903 blood samples from 7157 healthy men and women were pooled and analysed by generalised estimating equation (GEE) models. Adjusted normal ranges of haematological parameters were calculated for Blacks and Non-blacks.

RESULTS: Results show statistically significantly higher rises in total WBC and sub cell population counts (neutrophils, monocytes and basophils) between 08:00 and 18:00 for both black and non-black. Results demonstrate a diurnal pattern of white cell counts (Figure 1). Counts of various leucocytes were consistently higher than from black subjects. Total WBC counts as well as neutrophil, lymphocyte and monocyte counts showed increases of 24%, 36%, 16%, and 9%, respectively over the day.

CONCLUSION: Ethnicity and sampling time of day should be taken into account when interpreting WBC levels. We propose the adoption of ethnic specific Reference Intervals (RIs) for common laboratory tests and that considerations be given to these different ranges when determining trial inclusion criteria, as well as in the assessment of adverse events, including the relationship to the investigational product.



14.25 – 14.35

3.2 Do we need pharmacokinetic data during each data review meeting in adaptive first-in-human trial? From guideline to practice

Nariné Baririan[1,2]
Lien Gheyle[2], Frédéric Vanhoutte
[1]Club Phase 1 (AFPT), [2]BAPU

BACKGROUND/PURPOSE: The revised version of EMA guideline on first-in-human (FIH) trials highlights the importance of pharmacokinetic (PK) and pharmacodynamic data review at different stages of adaptive FIH trials. Our paper aims to analyse how PK data are used in practice during this review process and how this can be improved.

METHODS: Data on the clinical study database of our Clinical Pharmacology Unit (CPU) was used to retrieve all FIH trials performed between 2010 and 2018. The timing/nature of intermediate PK analysis and its influence on dose decisions was analysed.

RESULTS: All 43 studies included PK data during the review process. In 50% of cases one of the reasons of design/conduct change was PK, frequently requiring a substantial/non-substantial protocol amendment. Of these reasons, we can mention unexpected long half-life, above-dose proportionality, predefined drug exposure limit reached, high inter-subject variability of PK. Frequent design/conduct changes due to PK involve inclusion of additional doses/subjects, decrease or increase of dose, assessment(s) timepoints change, prolongation of follow-up period. In 18% of cases, the study was stopped due to PK findings. In 14 studies, the blinded PK analysis was performed after each single and/or multiple doses.

CONCLUSIONS: Inclusion of PK data in review steps increased over the last 10 years. We acknowledge the consequences it may have on further development process of the IMP; however, a more tailored review may increase the cost-effectiveness whilst keeping the crucial information.

14.35 – 14.45

3.3 Impact of cholinergic tone on the binding of PET Tracer [^{11}C]MK-6884, a positive allosteric modulator of M4 acetylcholine receptor in monkeys and healthy elderly volunteers

Inge De Lepeleire[1]

T. Bueters[2], A.M. Hussain[2], Y. Wang[2], T.G. Lohith[2], H.D. Haley[2], M.L. Purcell[2], M.A. Holahan[2], E.D. Hostetler[2], P.J. Coleman[2], R.D. Mazzola Jr.[3], L. Tong[3], J.A. Morrow[2], J.M. Uslaner[2], G. Bormans[4], M. Koole[5], K. Van Laere[5], K. Serdons[4], A. Van Hecken[6], J.N. de Hoon[6], C. Vandermeulen[6], R. Declercq[1], Y. Li[2], A.S. Basile[2], W. Li[2];

[1]Translational Pharmacology Europe, Merck Sharp & Dohme (Europe) Inc., Brussels, Belgium.[2]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Westpoint, PA, USA, [3]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Kenilworth, NJ, USA, [4]Department of Radiopharmacy, K.U. Leuven, Leuven, Belgium, [5]Division of Nuclear Medicine, K.U. Leuven and University Hospital Leuven, Leuven, Belgium, [6]Center for Clinical Pharmacology, K.U. Leuven, Leuven, Belgium.

BACKGROUND: [11C]MK-6884 is a positive allosteric modulator of muscarinic M4 acetylcholine (ACh) receptors (M4 PAM) that is being developed as a novel PET tracer to facilitate development of therapeutic drugs for Alzheimer's disease (AD). AD patients are frequently treated with acetylcholinesterase inhibitors, which increase brain ACh concentrations. These changes can alter binding of M4 PAMs to their binding sites through allosteric mechanisms. The current studies evaluated the indirect, allosteric modulatory effects of donepezil on binding of [11C]MK-6884 to the M4 PAM site.

METHODS: Donepezil (0.1-0.3 mg/kg i.m.) was administered to Rhesus monkeys (N=4) 60 min prior to administration of [11C]MK-6884. Brain PET scans were collected for 90 mins and striatal non-displaceable binding potential (BPND) was determined. In a Phase 1 open-label, two-cohort study, healthy elderly volunteers (HEVs; N=8, aged 57-64 yrs) received a titration regimen of oral donepezil: 5 mg QD for 7 days followed by 10 mg QD for 14 days. PET scans were acquired at pre-treatment, 4 or 9 days into, and at the end of donepezil treatment. Striatal BPND was calculated. The human study design was informed by a developed literature-based PK/PD model of donepezil.

RESULTS: Donepezil increased BPND of [11C]MK-6884 in Rhesus and HEVs in a concentration-dependent fashion, consistent with the influence of cholinergic tone on [11C]MK-6884 binding. The increase in striatal BPND was more pronounced in monkey than human.

CONCLUSION: This observation indicates that [11C]MK-6884 can measure the ACh tone change in monkey and human. [11C]MK-6884 enables non-invasively monitoring of ACh tone in vivo in human brain. This data allows development of a model that would inform dose adjustments of M4 PAM compounds in AD patients who are taking AChEI, thereby avoiding development of adverse events while providing maximal efficacy.

14.45 – 14.55

3.4 Outcome of patients participating in early phase oncology trials at the Drug Research Unit Ghent (D.R.U.G.), Belgium.

Brant Delafontaine[1,2]

Griet Van Lancker[1,3]; Carla Vandenabeele[1]; Sylvie Rottey[1,3,4]

[1]Drug Research Unit Ghent, Ghent University Hospital, Ghent, Belgium., [2]Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium., [3]Heymans Institute for Pharmacology, Ghent University, Ghent, Belgium., [4]Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium.

INTRODUCTION: Patients suffering from advanced solid tumours for whom standard therapy is not effective or not appropriate, and who are still in good general condition, can be considered for participation in an early phase trial with investigational medicinal products (IMPs).

RESEARCH QUESTION: What can be expected with regard to outcome in early phase oncology trials?

METHODS: Data from patients with advanced solid tumours who started therapy in an oncology trial between 01-Jan-2017 and 31-Jul-2018 at D.R.U.G. were collected. Data contained baseline parameters, information on IMP, and outcome.

RESULTS: Fifty-two patients with a wide range of advanced solid tumours started treatment in an early phase trial. Baseline characteristics and tumour types are shown in Table 1 and Figure 1, respectively. Experimental treatment consisted of a regimen including an anti-PD(L)1 immune checkpoint inhibitor in the majority of cases. The remaining drug categories were other immunotherapies, antibody-drug conjugates, and oral targeted agents (Figure 2). Median progression-free survival (PFS) in this population was less than 2 months (Figure 3), although 16% of patients remained free of progression beyond 6 months of initiation of IMP. The main reason for patients to discontinue study was progressive disease (PD) based on (i)RECIST and/or clinical progression (Figure 4).

CONCLUSION: The majority of oncology patients who participate in an early phase trial discontinued within 2 months because of PD. A small group of patients experience benefit for a long period of time. These results reinforce participation to an early phase clinical trial is a reasonable approach for oncology patients who lack treatment options. The relative small group of patients with prolonged PFS underlines the need to improve patient selection and for predictive biomarkers for new (immuno-)oncology drugs.

Table 1: Baseline characteristics	
Period:	01 Jan 2017 till 31 Jul 2018
Number of patients:	52
Age at inclusion (median, min-max):	62 years (40 – 80)
M:F ratio	44% - 56%
Number of previous systemic treatments (median, min-max):	2 lines (1 – 7)

FIGURE 1

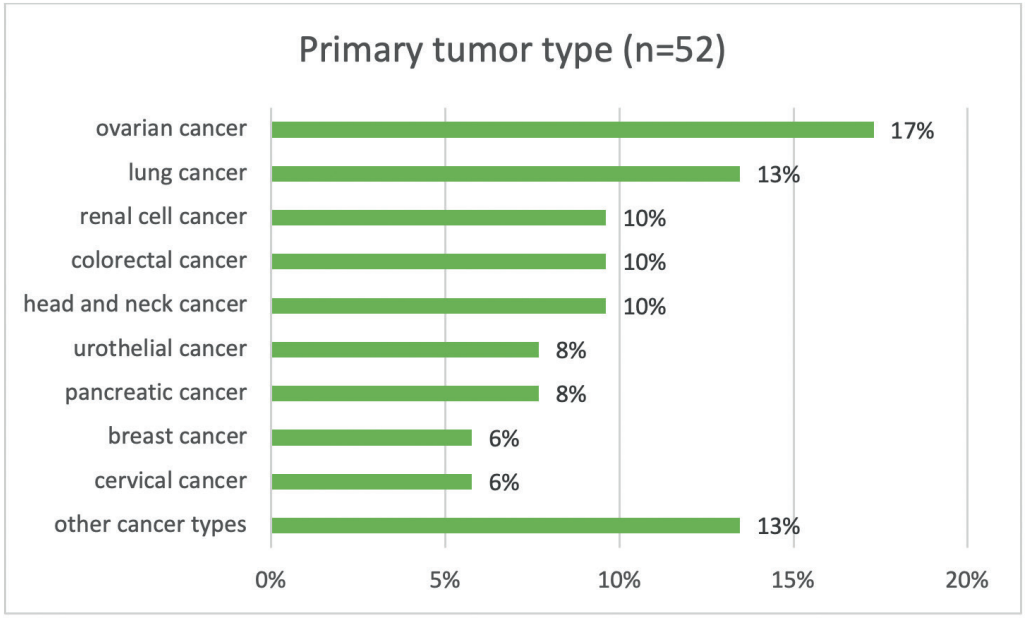


FIGURE 2

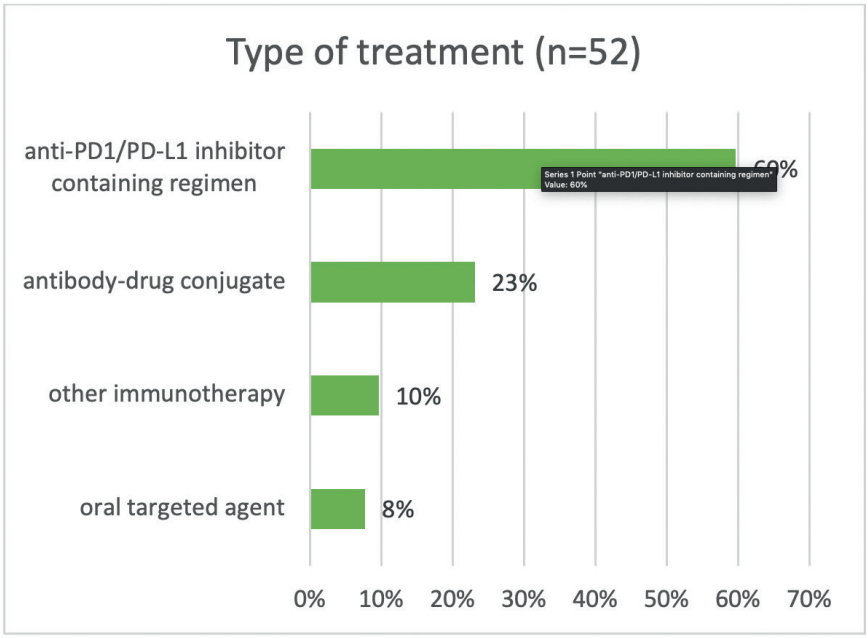


FIGURE 3

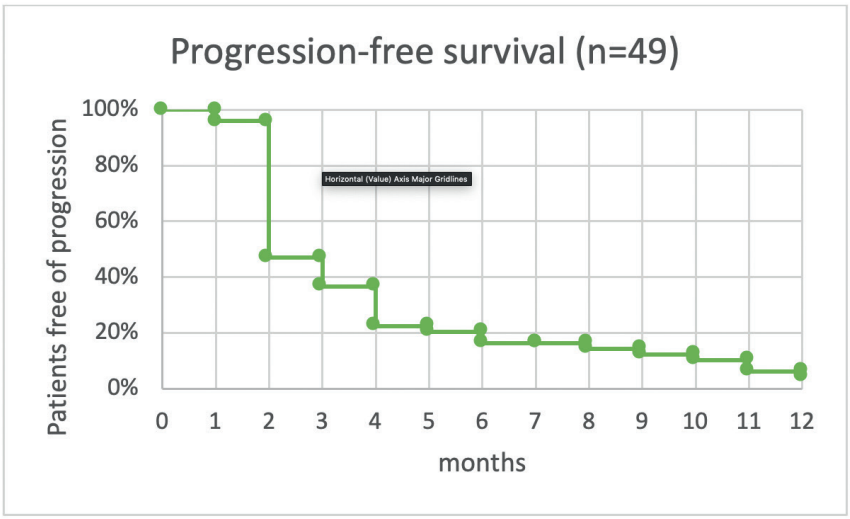
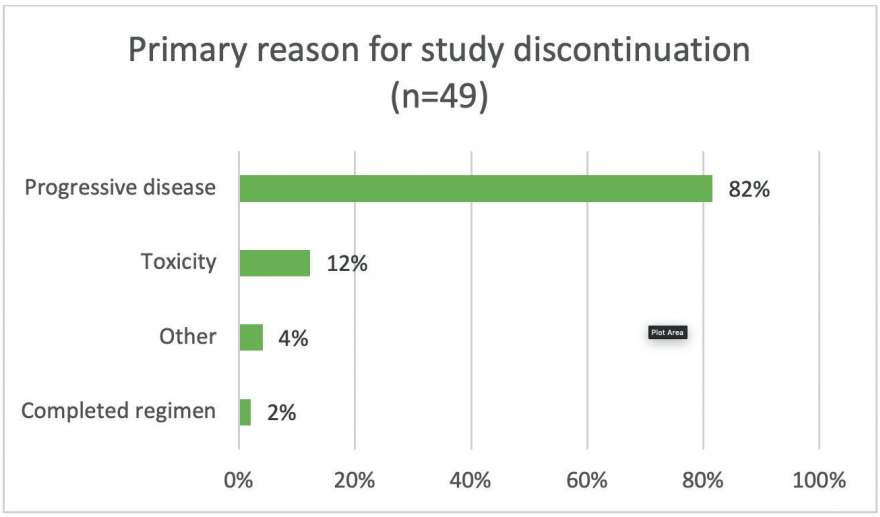


FIGURE 4



14.55 – 15.05

3.5 Volumetric absorptive microsampling (VAMS) for blood collection in clinical studies of padsevonil

Hugues Chanteux[1]

Christian Otoul[1], Gregory Lelij[2], Chiara Rospo[1], David Sciberras[1], Bart Van Den Steen[3]

[1]UCB Pharma, Braine-l'Alleud, Belgium; [2]Pauwels Consulting, Brussels, Belgium; [3]Novellas Healthcare, Zellik, Belgium

BACKGROUND: Volumetric Absorptive Microsampling (MITRA, Volumetric Absorptive MicroSampling - VAMS™) is a novel technique that enables accurate and precise collection of small (10 uL) blood volumes by dipping the absorbent MITRA microsampler tip into a blood bead after skin prick (Figure 1). The MITRA is then allowed to air-dry and is stored at room temperature pending subsequent bioanalysis. The objective is to implement, for a new drug candidate (padsevonil), the use of MITRA for collection of blood samples and evaluate it throughout bioanalytical assays and clinical trials.

METHODS: After feasibility evaluation, the strategy for MITRA implementation in a global clinical programme, investigating padsevonil (PSL) in epilepsy, has included: validation according to FDA and EMA guidance of an liquid chromatography-tandem mass spectrometry method for PSL analysis in blood using MITRA, and bridging of PSL concentration data in plasma and whole blood in both healthy subjects (n=28) and patients with epilepsy (n=14).

RESULTS: Bioanalytical assay performance was within criteria, confirming precision and accuracy over a clinically relevant blood concentration range (2-2000ng/mL), selectivity against major PSL metabolite and co-administered drugs, no carry over or matrix effects, long-term temperature stability, and no impact on haematocrit. MITRA blood sampling showed good correlation between blood and plasma (0.91-0.98) and approximately 35% lower PSL exposure compared with venous sampling, in close agreement with in vitro blood to plasma ratio of 0.7.

CONCLUSIONS: These data suggest that MITRA is a valid method for measuring the drug exposure during a clinical trial or in clinical practice. This alternative method for venous sampling reduces burden for patients and healthcare providers as well as reducing cost by improving logistical efficiency.

FIGURE 1

Parallel Breakout Sessions

16.00 – 17.30

1. Digital support to study performance in early phase development – from recruitment to remote data collection

Mr Robert Rissmann - Leiden University Medical Centre, The Netherlands and Ingrid Klingmann - PHARMAPLEX bvba, Belgium

The current breakthrough of mobile technologies in daily life are a major opportunity for the redesign of clinical trials. The intensive in clinic visits of trials can gradually change to the patients' home setting with more 'real world' information. Almost all parameters can be monitored comprehensively including vital signs, movement patterns, social behaviour, activity, specific symtoms such as tremor, as well as treatment adherence, symptom diary etc. In order to enable this reliable tools and applications are necessary. This session will discuss technological implications for novel methodologies and mobile apps. In addition regulatory aspects will be touched upon as well as lessons for early phase clinical research.

16.00 – 17.30

2. Lay summary requirements – consequences for Phase I trials

Dr Kerstin Breithaupt-Gröegler, Germany and Dr Leonie Leithold - Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Abstract not available at time of print.

16.30 – 17.30

3. Transparency requirements for Phase I trials in times of transition

Prof. Dr. Gerhard Koëter Netherlands and Dr Sander van den Bogert - Apotheek Boekel, Netherlands

Transparency is currently a major topic of debate in clinical research. Increasingly, companies are required to register clinical drug trials in advance in public registries. This break-out session will cover recent research into how phase I trials are performing in terms of transparency compared to later-phase trials, and why phase I trials in oncology are doing better. A brief overview will be provided of the current legal requirements and of expected future changes in transparency policies with the implementation of the new EU regulation and portal.

Can too much transparency harm the business model of the industry? What is the definition of commercially confidential information? Should it be required to publish the clinical trial protocol and investigator's brochure in public? Is there still a role for the classical method of transparency (i.e. journal publication), or should we use social media instead? The ultimate aim of this break-out session is to combine our knowledge and the perspectives of the audience as the two ingredients for having an interactive discussion about these and other issues in transparency.

16.00 – 17.30

4. What is acceptable/ethical to test in healthy subjects?

Prof. Dr. Sylvie Rottey - Drug Research Unit Ghent (D.R.U.G.), Belgium and Professor Dr Jan de Hoon - University of Leuven / University Hospitals Leuven, Belgium

Abstract not available at time of print.

Friday 17 May

09.00 – 09.20

MHRA perspective

Mr Ian Rees, UK

Abstract not available at time of print.

09.20 – 09.40

EMA perspective

Mr Fergus Sweeney - European Medicines Agency, Netherlands

Abstract not available at time of print.

09.40 – 10.00

Industry perspective

Mr Nick Sykes, Pfizer, UK

Abstract not available at time of print.

Session 5: How to be prepared

13.15 – 13.45

Phase I trials in patients: new approaches and designs in Oncology

Dr Nuria Kotecki - Jules Bordet Institute, Belgium

Advances in the understanding of tumor biology have changed the landscape of clinical research and resulted in evolving treatment strategies such as precision medicine implying the use of targeted agents and activating the immune system against cancer using immunotherapy. The move from empirical cytotoxic to molecular and immunological therapeutic approaches has impacted clinical trial designs. For example, adapted study designs, dose-limiting toxicities definitions and endpoints have been proposed, but are still underused. The presentation will focus on innovative strategies, approaches and study designs in early drug development in oncology.

13.45 – 14.15

Challenges in exploratory clinical research

Dr Maarten Van den Boer - Janssen Pharmaceutica, Belgium

Exploratory Clinical Research is transforming. Trial design and execution becomes more complex through high degrees of innovation. There is a high need for early data readout in the patient population to reduce the overall drug development cost and timelines. Getting patients in early phase 1 trials turns out to be very challenging. These recruitment problems can be protocol, patient and investigator related. Can these recruitment problems be identified? Should we change the way we use to work? This presentation will point out a few possible approaches of how early phase patient could be managed and executed.

14.15 – 14.45

Current perspectives on digital biomarker development in early clinical research

Ms Virginia Parks - Takeda, USA

The implementation of wearable technology (WT) in clinical drug development programs is an emerging field in medical research. It enables the noninvasive collection of real-time objective data in a patient's natural setting to enhance our understanding of the effects of treatment and how symptoms may change over time. Combined with predictive analytical techniques such as machine learning, WT promises to contribute to the advancement of innovative therapeutics as effective treatment solutions through novel endpoint, or digital biomarker discovery.

Although there is much enthusiasm for its use in medical research, more rigorously produced data is needed for the field to progress and to establish valid methodologies. The considerations and challenges for development of a novel digital biomarker are discussed, and how these pertain to clinical pharmacologists and pharmacometricians who are frequently involved in decision-making on the right dose, right patient, study design, and trial progression.

Many insights can be garnered from the use of WT, as illustrated by recent case study examples e.g., digitally acquired motor symptom data in Parkinson's Disease (PD). However, it is noted that most of the data currently being produced is from observational, non-randomized small-scale studies without placebo control.

There are therefore real and perceived scientific and operational challenges related to the implementation of a digital biomarker strategy in early clinical development. The obstacles to greater adoption and acceptance are discussed, including current regulatory guidelines, frameworks for industry, and thoughts for future developments in this nascent field of research.

POSTER LIST

P1 **Also presented as oral 3.1**	**Diurnal and ethnic variance of white blood cell parameters in early phase clinical trials: a retrospective analysis of pooled data from multiple phase I trials** **Simon Coates**[1], Sara Fernandes[1], Duolao Wang[2], Clare Umukoro[1], Dilshat Djumanov[1], Ulrike Lorch[1], Jörg Täubel[1 3]. [1]Richmond Pharmacology, St George's, University of London, UK [2]Department of Clinical Sciences, Liverpool School of Tropical Medicine, UK [3]St George's, University of London, UK
P2	**Efficient design of integrated and adaptively interlinked early phase drug development programs** **Simon Coates**[1], Oliver Pohl[2], Jean-Pierre Gotteland[2], Jörg Täubel[1], Ulrike Lorch[1] [1]Richmond Pharmacology, [2]ObsEva SA
P3	**Pharmacokinetics and Safety of the Oral Prostaglandin F2α Receptor Antagonist OBE022: A First-In-Human Study in Healthy Post-Menopausal Women** **Simon Coates**[2], Oliver Pohl[1], Line Marchand[1], Jean-Pierre Gotteland[1], Jörg Täubel[2], Ulrike Lorch[2] [1]ObsEva SA, [2]Richmond Pharmacology
P4	**The pharmacokinetic interaction of the selective PGF2α receptor antagonist OBE022 on co-administration with $MgSO_4$, atosiban, nifedipine or betamethasone** **Simon Coates**[2], Oliver Pohl[1], Line Marchand[1], Jean-Pierre Gotteland[1], Jörg Täubel[2], Ulrike Lorch[2] [1]ObsEva SA, [2]Richmond Pharmacology
P5	**Practical risk management for adaptive integrated early phase clinical trials** **Jörg Täubel**[1], Simon Coates[1], Ulrike Lorch[1] [1]Richmond Pharmacology
P6	**Comparison of ECG parameters using GE GETEMED continuous ECG Holter and MAC-1200 bedside ECG** **Jörg Täubel**[1], Sara Fernandes[1], Boaz Mendzelevski[2], Dilshat Djumanov[1], Georg Ferber[3] [1]Richmond Pharmacology, [2]Cardiac Safety Consultants Ltd, [3]Statistik Georg Ferber GmbH
P7	**Concentration-Effect Modelling of Blood-Pressure in Early Stage Trials** **Jörg Täubel**[1], Ulrike Lorch[1], Georg Ferber[2] [1]Richmond Pharmacology, [2]Statistik Georg Ferber GmbH
P8	**Concentration-QTc analysis integrated into a Phase 1 bridging study in healthy Caucasian and Japanese subjects** **Jörg Täubel**[1], Ulrike Lorch[1], Simon Coates[1], Dilshat Djumanov[1], Georg Ferber[2] [1]Richmond Pharmacology, [2]Statistik Georg Ferber GmbH
P9 **Also presented as oral 3.2**	**Do we need pharmacokinetic data during each data review meeting in adaptive first-in-human trial? From guideline to practice** **Nariné Baririan**[1,2]; Lien Gheyle[2]; Frédéric Vanhoutte [1]Club Phase 1 (AFPT), [2]BAPU
P10	**Biologics and Biosimilars Drug Development: Low-Dosing Requirements and Strategies for Matching Bioanalytical Study Support** **Mark Spengler**[1] [1]Chimera Biotec

P11 **Also presented as oral 3.3**	**Impact Of Cholinergic Tone On The Binding Of PET Tracer [11C]MK-6884, A Positive Allosteric Modulator Of M4 Acetylcholine Receptor In Monkeys And Healthy Elderly Volunteers** **I. De Lepeleire**[1], T. Bueters[2], A.M. Hussain[2], Y. Wang[2], T.G. Lohith[2], H.D. Haley[2], M.L. Purcell[2], M.A. Holahan[2], E.D. Hostetler[2], P.J. Coleman[2], R.D. Mazzola Jr.[3], L. Tong[3], J.A. Morrow[2], J.M. Uslaner[2], G. Bormans[4], M. Koole[5], K. Van Laere[5], K. Serdons[4], A. Van Hecken[6], J.N. de Hoon[6], C. Vandermeulen[6], R. Declercq[1], Y. Li[2], A.S. Basile[2], W. Li[2] [1]Translational Pharmacology Europe, Merck Sharp & Dohme (Europe) Inc., Brussels, Belgium.[2]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Westpoint, PA, USA, [3]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc, Kenilworth, NJ, USA, [4]Department of Radiopharmacy, K.U. Leuven, Leuven, Belgium, [5]Division of Nuclear Medicine, K.U. Leuven and University Hospital Leuven, Leuven, Belgium, [6]Center for Clinical Pharmacology, K.U. Leuven, Leuven, Belgium.
P12 **Also presented as oral 3.4**	**Outcome of patients participating in early phase oncology trials at the Drug Research Unit Ghent (D.R.U.G.), Belgium.** **Brant Delafontaine**[1,2], Griet Van Lancker[1,3], Carla Vandenabeele[1], Sylvie Rottey[1,3,4] [1]Drug Research Unit Ghent, Ghent University Hospital, Ghent, Belgium., [2]Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium., [3]Heymans Institute for Pharmacology, Ghent University, Ghent, Belgium., [4]Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium.
P13	**Challenges and opportunities of academic phase I trials using the example of two vaccination trials (Ebola and Mers CoV)** **Saskia Borregaard**[1], Christine Dahlke[2,3,4], Marylyn M. Addo[2,3,4] [1]CTC North GmbH & Co. KG, Hamburg, Germany [2]University Medical Center Hamburg-Eppendorf, 1stDepartment of Medicine, Division of Infectious Diseases, Hamburg, Germany [3]Department for Clinical Immunology of Infectious Diseases, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany [4]German Center for Infection Research, partner site Hamburg-Lübeck-Borstel-Riems
P14 **Also presented as oral 3.5**	**Volumetric Absorptive Microsampling (VAMS) for Blood Collection in Clinical Studies of Padsevonil** **Hugues Chanteux**[1] (Oral), **Christian Otoul**[1] (Poster), Gregory Lelij[2], Chiara Rospo[1], David Sciberras[1], Bart Van Den Steen[1] [1]UCB Pharma, Braine-l'Alleud, Belgium [2]Pauwels Consulting, Brussels, Belgium [3]Novellas Healthcare, Zellik, Belgium
P15	**Transient receptor potential channels as possible targets for paracetamol and metamizole: translation from bench to bedside** **Dorien Bamps**[1], Heleen Marynissen[2], Laura Macours[2], Linde Buntinx[2], Jan de Hoon[2] [1]KU Leuven, [2]UZ Leuven
P16	**Refining a scopolamine biomarker platform for cognitive impairment** **An Bautmans**[1], Sarah Janicki Hsieh[2], Florestina Telan-Choing[2], Anran Wang[2], Lien Gheyle[3], Hilde Baelus[3], Claire Li[2], Inge De Lepeleire[1], Mark Forman[2], Aubrey Stoch[2] [1] Merck Sharp and Dohme, Europe Inc., Brussels, Belgium [2] Merck & Co., Inc., Kenilworth, New Jersey, U.S.A [3] SGS Life Science Services, Antwerpen, Belgium
P17	**A REcommander System to Enhance Drug Development in oncology from phase I trials: the RESOLVED2 project** **Loic Verlingue**[1], Beinse Guillaume[1], Christophe Massard[1], Isabelle Borget[1], Antoine Hollebecque[1] [1]Institut Gustave Roussy

POSTER PRESENTATION ABSTRACTS

P1 Diurnal and ethnic variance of white blood cell parameters in early phase clinical trials: a retrospective analysis of pooled data from multiple phase I trials

See 3.1, page 33.

P2 Efficient design of integrated and adaptively interlinked early phase drug development programs

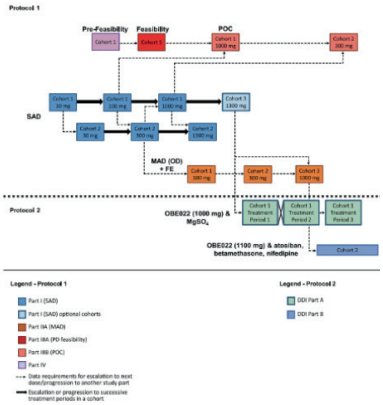
Simon Coates[1], Oliver Pohl[2], Jean-Pierre Gotteland[2], Jörg Täubel[1], Ulrike Lorch[1]

[1]Richmond Pharmacology, [2]ObsEva SA

BACKGROUND: Current practice favours integrated protocols in early phase clinical trials. Adaptively combining clinical trial protocols provides advantages in increasing participant safety, effective data collection as well as increasing the speed of clinical development programs completion. This work describes the integration of an early development program for a novel, oral, selective prostaglandin F2a receptor antagonist, intended as a treatment for preterm labour using two interdependent, adaptive trial protocols.

METHOD: The program consisted of first-in-human single and multiple ascending dose of OBE022 (SAD and MAD) with assessments of food effect (FE), cardiac safety, a separate feasibility assessment, proof of concept (POC), and interactions of OBE022 with four standard of care medicines (DDI). Two interdependent, adaptive trial protocols were used (Figure 1).

RESULTS: Study parts were designed to overlap – the MAD, FE, POC and DDI were initiated once relevant dose levels/exposures had been tested. The feasibility cohort to optimise the technique of intrauterine pressure catheter placement prior to their use in the POC part used an active control only, and thus commenced in parallel with the SAD. Considering the distinct risk assessment needed, and the later time point at which the DDI would start, this aspect of the study was split from the main FIH protocol into a separate study. The adaptive design resulted in significant time savings and a reduced number of subjects than originally planned. The overall program took 11 months. Eighty subjects were included.



CONCLUSIONS: This program included all key elements of early drug development in two interlinked protocols. The approach described demonstrates how early-phase programs can be designed to be performed, analysed and reported time- and cost-efficiently.

P3 Pharmacokinetics and Safety of the Oral Prostaglandin F2α Receptor Antagonist OBE022: A First-In-Human Study in Healthy Post-Menopausal Women

Simon Coates[2], Oliver Pohl[1], Line Marchand[1], Jean-Pierre Gotteland[1], Jörg Täubel[2], Ulrike Lorch[2]

[1]ObsEva SA, [2]Richmond Pharmacology

BACKGROUND: Preterm birth remains a significant risk for later disability. The selective inhibition of the prostaglandin F2α (FP) receptor has tocolytic activity and offers significant clinical advantages over other tocolytic pathways. The pro-drug OBE022 and its parent metabolite OBE002 are novel FP receptor antagonists currently under development for treating preterm labour. This early phase trial investigated the safety, tolerability and pharmacokinetics of OBE022 in healthy postmenopausal female subjects.

METHODS: This was a first in human, dose-escalation, placebo-controlled, randomised trial. Single ascending doses of 10, 30, 100, 300, 1000 or 1300 mg OBE022, and multiple ascending doses over seven days of 100, 300 or 1000 mg/d were administered to 36 post-menopausal female volunteers. Blood samples were collected for PK analysis for up to 144 hours after OBE022 administration.

RESULTS: OBE022 was safe and well tolerated at all single and multiple doses. OBE022 was readily absorbed and rapidly converted into its equally active stable metabolite OBE002. Plasma levels of OBE002 rose with increasing doses of OBE022 reaching exposure levels anticipated to be clinically relevant within 1 hour following administration. There was no clinically relevant interaction with food. The mean t½ of OBE002 ranged between 8 and 11 hours following administration of a single dose and between 22 to 29 hours after multiple doses.

CONCLUSIONS: Single or repeated oral daily administration of OBE022 has a favourable pharmacokinetic profile (characterised by t½, distribution and dose proportionality) and no safety concerns when dosed at 1000 mg per day in multiple doses and up to 1300 mg per day in single doses. The pharmacokinetic values and safety profile fulfil the requirements for advancement to further clinical testing of OBE022 as tocolytic in preterm labour patients.

P4 The pharmacokinetic interaction of the selective PGF2α receptor antagonist OBE022 on co-administration with $MgSO_4$, atosiban, nifedipine or betamethasone

Simon Coates[2], Oliver Pohl[1], Line Marchand[1], Jean-Pierre Gotteland[1], Jörg Täubel[2], Ulrike Lorch[2]

[1]ObsEva SA, [2]Richmond Pharmacology

BACKGROUND: Preterm birth is a major cause of perinatal mortality and morbidity. OBE022 is a novel, prostaglandin F2α receptor antagonist under development for treatment of preterm labour. In clinical practice, tocolytics are co-administered with betamethasone for lung maturation and MgSO4 for neuroprotection. Tocolytic drugs of different modes of action may be used in combination to increase efficacy, without adversely affecting the mother or foetus.

METHODS: This was an open-label, randomised, three-period crossover study assessing the pharmacokinetics of the co-administration of OBE022 (1100 mg) and MgSO4 (15.5 g) in 12 healthy premenopausal women. An open-label, single sequence crossover study assessing the interactions of single doses of OBE022 (1000 mg/day) at steady-state co-administered with atosiban (60.75 mg), nifedipine (20mg) and betamethasone (12 mg) in 12 healthy premenopausal women was also performed.

RESULTS: There were no pharmacokinetic interactions between OBE022 and MgSO4. Neither OBE022 or MgSO4 pharmacokinetics were affected. OBE022 had no effect on atosiban. However, atosiban slightly reduced exposure to OBE002, the pharmacologically active metabolite of the pro-drug OBE022 (Cmax, -28%; AUC, -21%). OBE022 co-administered with betamethasone slightly increased betamethasone exposure (Cmax, +18%; AUC, +27%) and that of OBE022 (Cmax, +30%; AUC, +15%). These changes were not considered clinically relevant. OBE022 co-administered with nifedipine slightly increased OBE002 exposure (Cmax, +29%; AUC, +24%) and markedly increased nifedipine exposure (Cmax, +133%; AUC, +137%). All drugs, alone or in combination, were well tolerated.

CONCLUSIONS: There were no clinically relevant pharmacokinetic interactions between OBE022 and MgSO4, betamethasone, or atosiban, whereas nifedipine exposure doubled when co/administered with OBE022. Co-administration of OBE022 with MgSO4, betamethasone and tocolytic drugs could be an effective strategy for preventing/delaying preterm delivery.

P5 Practical risk management for adaptive integrated early phase clinical trials

Jörg Täubel[1], Simon Coates[1], Ulrike Lorch[1]

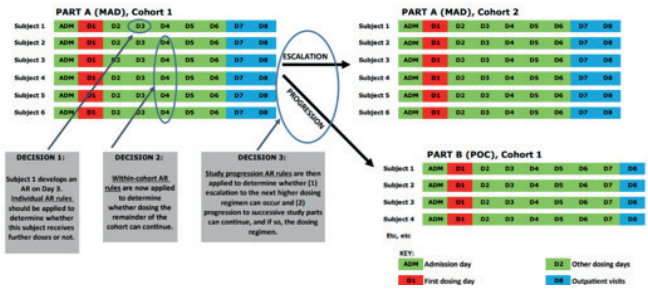
[1]Richmond Pharmacology

BACKGROUND: Risk management is an essential element of integrated, adaptive early phase protocols. Toxicities are major factors determining whether a study continues or is suspended, thus any rules regarding toxicities will significantly define study structure and progression. The revision to the European Medicines Agency's first-in-human and early phase clinical trials guideline mandates the use of unambiguous rules for severe and serious adverse reactions (AR). Methodology for designing rules for healthy volunteer and patient trials in investigational or marketed medicinal products are presented.

METHODS: Template rules were developed using standard NCI CTCAE terminology and a systemic, objective, and consistent process. Severity, seriousness, frequency, and reversibility or ARs were considered. These rules control decisions related to individual trials participants, dosing regimens and to dose escalation and/

or progression to successive trial parts. Trial-specific adaptations were made based on properties of the investigational medicinal products (IMP), non-IMP, Reference Safety Information (RSI) and the degree of uncertainty about potential ARs.

RESULTS: The template AR rules have been successfully applied to many early phase adaptive integrated trials authorised by the MHRA and performed in the UK. This work presents the template rules table and case studies of some trial-specific adaptations. Figure 1 shows the principle of how template rules were created and applied



in an integrate trialto reflect three decisions, ensuring that the assessment of ARs occurred in a systematic order..

CONCLUSIONS: This template demonstrates how systematic, objective, and consistent risk management of large integrated trials accommodating multiple concurrent trial arms or parts, can be simple yet robust, facilitate effective decision making and ensure participant safety. This template can be adapted for specific IMPs or trials if necessary, taking into account anticipated effects. It fulfils regulatory requirements and has been tried and tested, having been approved and used for many trials in the UK.

P6 Comparison of ECG parameters using GE GETEMED continuous ECG Holter and MAC-1200 bedside ECG

Jörg Täubel[1], Sara Fernandes[1], Boaz Mendzelevski[2], Dilshat Djumanov[1], Georg Ferber[3]

[1]Richmond Pharmacology, [2]Cardiac Safety Consultants Ltd, [3]Statistik Georg Ferber GmbH

BACKGROUND: In clinical trials, only a limited number of ECG recordings can be performed and therefore, long intervals may elapse between assessment timepoints. These limitations have led to the frequent use of Holter recorders to collect continuous data and placing much less burden on patients and freeing up staff conducting trials. However, there is limited data comparing the two approaches.

METHODS: Data from a randomised, double-blind four-period crossover Thorough QT (TQT) study in 40 healthy subjects were selected for analysis [1]. Continuous 12L Holter was recorded in parallel to standard 12L 10s bedside ECG using dual leads thereby recording the exact same signal. Heart rate and QT interval estimates were extracted by averaging three consecutive beats. Values exceeding sample average by more than 5% were tagged as outliers and excluded from the analysis. Holter values were extracted as close to the conventional ECG timepoint as possible and manually adjudicated by an experienced cardiologist.

RESULTS: Visual assessment of the Holter signal showed a good correlation with bedside ECGs collected at correspondent timepoints. Holter outputs also showed well defined meal-induced QTcF reductions between 6 and 12 hours that were not detected by bedside ECGs. Manual adjudication, for adjusting the Holter estimates significantly, improved correlation, both at the individual and at the general level.

CONCLUSIONS: Continuous ECG recordings can provide a more accurate reflection of ECG changes over a 24-hour time period than bedside ECGs. Manual adjudication is essential to ensure that only artefacts are correctly identified and removed, and no ‘true’ signals are filtered out.

P7 Concentration-Effect Modelling of Blood-Pressure in Early Stage Trials

Jörg Täubel[1], Ulrike Lorch[1], Georg Ferber[2]

[1]Richmond Pharmacology, [2]Statistik Georg Ferber GmbH

BACKGROUND: Drug-induced hypertension is a serious toxic effect of several medication classes such as sympathomimetics, corticosteroids, and vasoconstrictors. Assessment of a concentration-effect relationship for investigational medicinal products is valuable where vascular effects are possible. Scientific and regulatory efforts to raise awareness and better define approaches for the assessment of blood pressure during drug development have been made [1]. This phase I study aimed to investigate the effect of a cholinomimetic agent being developed for use in Alzheimer’s disease on blood pressure.

METHODS: This was a randomised, multiple dose, placebo-controlled study in 30 male subjects (15 Japanese and 15 Caucasian). The study consisted of two treatment periods. The dose given in Treatment Period 2 was higher than that in Treatment Period 1. Subjects received either IMP Dose 1 or matching placebo on Period 1 Day 1, daily for 5 days (5 doses in total) and IMP Dose 2 or matching placebo on Period 2 Day 1. On Day 1 and Day 5, blood pressure was measured at -1.5 (pre-dose), 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hours. Concentration-effect analysis was used to investigate the relationship between the IMP and vital signs.

RESULTS: Analysis indicated a relationship between IMP concentration and blood pressure that was consistent with the mode of action a cholinomimetic agent. Some subjects experienced abnormal vital signs during the study; however, these were not prolonged, and none were judged to be clinically significant. No significant differences were detected between the different ethnicities in terms of the effect of the IMP on blood pressure.

CONCLUSIONS: This study supports the use of concentration-effect modelling to characterise blood pressure effects during phase I trials. The outcome of this approach would identify the presence of an important blood pressure effect sufficiently early in drug development. However, to classify the risk of a long therapy an extended study would be necessary

P8 Concentration-QTc analysis integrated into a Phase 1 bridging study in healthy Caucasian and Japanese subjects

Jorg Täubel[1], Ulrike Lorch[1], Simon Coates[1], Dilshat Djumanov[1], Georg Ferber[2]

BACKGROUND: Alzheimer's Disease (AD) is the most frequentcause of dementia. Currently, there is no cure for AD and the only treatments available target symptomatic relief. A cholinomimetic agent is being developed for the symptomatic relief of cognitive impairment in AD. This phase I study aimed to evaluate the effect of two doses of the IMP on the QT interval, using the effect of a meal on the QTc to confirm assay sensitivity.

METHODS: This was a randomised, multiple dose, placebo-controlled study with 30 healthy male subjects (15 Japanese and 15 Caucasian). The study consisted of two treatment periods. The dose given in Treatment Period 2 was 1.7x higher than that of Treatment Period 1. Subjects received either IMP Dose 1 or matching placebo on Period 1 Day 1, daily for 5 days (5 doses in total) and IMP Dose 2 or matching placebo on Period 2 Day 1. Serial ECG recordings and IMP concentration measurements were paired to allow concentration-QTc analysis. Assay sensitivity was assessed by means of the effect of the meal given 1 h before drug administration on Days 1 and 5 of both treatment periods.

RESULTS: The study met the criteria for a negative QT study, with the upper boundary of a two-sided 90% CI falling below 10 ms with respect to the doses tested. Differences between races were not significant. The sensitivity of the study to detect small changes in the QTc interval was confirmed by demonstrating a significant shortening of QTc after a standardized meal.

CONCLUSIONS: This study established that the cholinomimetic agent tested did not prolong the QTc interval. The observed food effect on the QT interval validated the assay on both assessment days.

P9 Do we need pharmacokinetic data during each data review meeting in adaptive first-in-human trial? From guideline to practice

See 3.2, page 34.

P10 Biologics and Biosimilars Drug Development: Low-Dosing Requirements and Strategies for Matching Bioanalytical Study Support

Mark Spengler[1]

[1]Chimera Biotec

BACKGROUND: Drug-induced hypertension is a serious toxic effect of several medication classes such as sympathomimetics, corticosteroids and vasoconstrictors, therefore assessment of a concentration-effect relationship for investigational medical products is valuable where vascular effects are possible. Scientific and regulatory efforts to raise awareness and better define approaches for the assessment of blood pressure during drug development have been made. [1] This Phase I study aimed to investigate the effect of a cholinomimetic agent being developed for use in Alzheimer's disease on vital signs.

METHOD: This was a randomized, multiple dose, placebo-controlled study with 30 male subjects (15 Japanese and 15 Caucasian). The study consisted of two treatment periods. The dose given in Treatment Period 2 was

higher than that of Treatment Period 1 by a factor of 1.7. On Days 1 and 5, vital signs were measured at -1.5, 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hours. Concentration-effect analysis was used to investigate relationship between the IMP and vital signs.

RESULTS: The concentration-effect analysis suggested a dependence of blood pressure on the plasma drug concentration, consistent with the mode of action of the IMP. Some subjects had isolated abnormal vital signs during the study: however, these were not prolonged, and none were judged to be clinically significant. No significant differences between races could be detected.

CONCLUSION: This study supports the use of concentration-effect modelling to quantify blood pressure effects during Phase I trials.

P11 Impact Of Cholinergic Tone On The Binding Of PET Tracer [^{11}C]MK-6884, A Positive Allosteric Modulator Of M4 Acetylcholine Receptor In Monkeys And Healthy Elderly Volunteers

See 3.3, page 34.

P12 Outcome of patients participating in early phase oncology trials at the Drug Research Unit Ghent (D.R.U.G.), Belgium

See 3.4, page 35.

P13 Challenges and opportunities of academic phase I trials using the example of two vaccination trials (Ebola and Mers CoV)

Saskia Borregaard[1], Christine Dahlke [2,3,4], Marylyn M. Addo [2,3,4]

[1]CTC North GmbH & Co. KG, Hamburg, Germany

[2]University Medical Center Hamburg-Eppendorf, 1stDepartment of Medicine, Division of Infectious Diseases, Hamburg, Germany

[3]Department for Clinical Immunology of Infectious Diseases, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany

[4]German Center for Infection Research, partner site Hamburg-Lübeck-Borstel-Riems

BACKGROUND: Investigator-initiated trials (IITs) provide tremendous opportunities for addressing and answering complex healthcare questions, as well as making an important contribution to the improvement of quality and efficiency of health services. However, the feasibility of IITs is highly depending on the phase of the trial. The 2010 report on innovation from the Office of Technology Assessment at the German Bundestag (TAB)1 clearly shows that the majority of IITs are being carried out in Phase III. However, academic phase I trials provide the chance to gather clinical data for new vaccines or drugs in an indication currently not the focus of a commercially directed research and to deliver important data to speed up the development of novel treatments and drugs highly needed for certain populations or regions.

METHOD: The aim of this abstract is to identify the challenges but also the opportunities of performing phase I IITs from the author´s experience with two academic vaccination trials: EBOLA and MERS CoV (NCT02283099, NCT03615911).

RESULTS: The Ebola crisis in West Africa in 2014 with over 28.000 cases and over 11.000 deaths2 demonstrated that untreated diseases with an epidemic potential represents a risk for the public health and underlined the importance of vaccine development for emerging infectious diseases independent from market potential. Academic phase I trials come along with challenges for the institutions taking over the sponsor role. Responsibilities are more extensive for studies with new drugs/vaccines not yet approved than for phase III trials. Work intensive long-term funding processes and duties not generally implemented within an academic environment (e.g. infrastructure for IMP release or IMPD writing) require a special focus and personal resources and competences. Close teamwork with the cooperating CRO and study site, preferable well experienced with investigator initiated trials helps to identify potential challenges at an early stage and provide necessary backing. The WHO Blueprint initiative for research and development (published in 2016)3 or the increasing provision of public funds for research in the field of emerging infections (e.g. Coalition for Epidemic Preparedness Innovations; www.cepi.net) show the raising awareness of the importance of academic early phase research.

CONCLUSION: Sufficient funding resources for early research and quick review timelines for proposals as well as essential infrastructure for phase I trials either within the academic institute or by a supporting CRO

well experienced with IITs are needed to strengthen the academic early phase research in order to ensure new treatments for emerging disease or indications with currently rare research focus.

1 Bührlen B, Georgieff P, Vollmar HC. Stand und Bedingungen klinischer Forschung in Deutschland und im Vergleich zu anderen Ländern unter besonderer Berücksichtigung nichtkommerzieller Studien [Internet] Januar 2010 Arbeitsbericht Nr. 135 Available from http://www.tab-beim-bundestag.de/de/pdf/publikationen/berichte/TAB-Arbeitsbericht-ab135.pdf

P14 Volumetric Absorptive Microsampling (VAMS) for Blood Collection in Clinical Studies of Padsevonil

See 3.5, page 37.

P15 Transient receptor potential channels as possible targets for paracetamol and metamizole: translation from bench to bedside.

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Despite their ubiquitous clinical use, exact mechanisms underlying the analgesic and antipyretic effects of paracetamol and metamizole remain undetermined. Recent preclinical evidence points in the direction of transient receptor potential vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) pathways as potential targets, yet in human evidence is lacking (1–5).

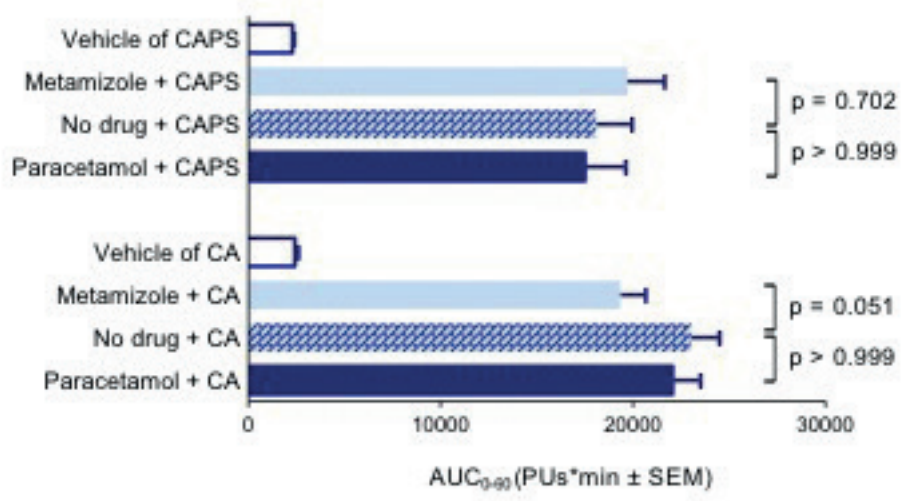
This study aims to unravel the clinical relevance of these results using human target engagement biomarkers for TRPV1 and TRPA1. By topically applying selective agonists, capsaicin (CAPS) for TRPV1 and cinnamaldehyde (CA) for TRPA1, a local vasodilatory response was evoked. Measuring this increase in dermal blood flow (DBF) provided a non-invasive approach to assess TRPV1 and TRPA1 interaction in vivo, in human (6,7).

Part I involved a randomized, double-blind, two-way cross-over study to address the acute effect of single oral doses of paracetamol (1 g) and metamizole (500 mg) in 16 healthy male volunteers. DBF was measured at baseline and 10, 20, 30, 40 and 60 minutes following application of CAPS (1000 µg/20 µL), CA (2 µL/20 µL) and vehicle solutions. Data was expressed as area under the curve over the 60 minutes period (AUC0-60) and analyzed using one-way repeated measures ANOVA with post-hoc Bonferroni adjustment.

The CA-induced DBF response was not influenced by paracetamol as there was no difference compared to no drug intake ($p > 0.999$ for AUC0-60). Metamizole tended to reduce the CA-induced DBF with a trend towards statistical significance ($p = 0.051$ for AUC0-60). The CAPS-induced DBF response was not affected by either paracetamol ($p > 0.999$ for AUC0-60) or metamizole ($p = 0.702$ for AUC0-60) compared to no drug intake (Fig. 1). To further investigate these effects, Part II has been set up to examine the influence of steady state concentrations of paracetamol (4 x 1g) and metamizole (4 x 500 mg) on TRPV1 and TRPA1. Recruitment is ongoing, but preliminary results are expected to be available at the time of the meeting.

FIGURE 1:

Influence of a single oral dose of paracetamol (1 g) and metamizole (500 mg) on the CAPS- and CA-induced DBF response (AUC0-60) in 16 healthy male subjects (one-way ANOVA with post-hoc Bonferroni).



P16 Refining a scopolamine biomarker platform for cognitive impairment

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OBJECTIVES: Scopolamine, a muscarinic acetylcholine receptor antagonist, induces cognitive impairment. Refining a scopolamine biomarker platform could provide early cognitive pharmacodynamic information for pro-cognitive compounds. Inter-subject variability in pharmacodynamic impairment response limits the value of doses ≤ 0.6 mg but relative absence of data at doses > 0.6 mg raises concerns for tolerability. Internal data demonstrates improved value following 0.8 mg preceded by a 0.5 mg dose to assess tolerability. However, this multiple-dose approach increases complexity in the platform. Therefore, the aim of this study was to confirm tolerability of a single subcutaneous dose of 0.8mg scopolamine.

METHODS: A study was conducted in sixteen healthy participants (n=12 active, n=4 placebo). Safety and tolerability was assessed by vital signs, cardiac telemetry monitoring, neurological examination, laboratory safety tests and AE reporting. Questionnaires assessing alertness and pharmacokinetic sampling were also employed.

RESULTS: Reported AEs were as expected and related to the pharmacological mechanism. Eleven subjects reported severe somnolence up to 3-6 hours post-dose. One participant on active drug experienced mild palpitations for 2 minutes that was not associated with changes in ECG tracings, and an idioventricular rhythm that lasted 3.5 hours. Questionnaires demonstrated greater sedation following scopolamine administration compared to placebo. Pharmacokinetic profile was found to be consistent with the label.

CONCLUSION: Administration of a single subcutaneous dose of scopolamine 0.8 mg did not demonstrate significant adverse events but was associated with a high frequency of somnolence and sedation. AEs were expected, transient and monitorable. This study shows that a single dose administration of scopolamine 0.8 mg provides a simplified approach to a well-characterized cognitive impairment model, thereby increasing the value of this platform for future use.

P17 A REcommander System to Enhance Drug Development in oncology from phase I trials: the RESOLVED2 project

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Drug development in oncology is facing a conjunction of increasing number of anti-neoplastic agents (ANA) candidate for phase 1 clinical trials (P1CT) and an important attrition rate for final approval. Machine learning methods may support drug development efficacy.

With data from PubMed abstracts and DrugBank5.0 database we trained a machine learning model to predict FDA approval. To this end, we have computed the Food & Drug Administration approval-free-survival (FDA-aFS). FDA-aFS is a right-censored variable defined by the time between first P1CT publication and the FDA approval date or censoring for compounds, up to 2018, July. Random split with a 70%/30% ratio allowed obtaining a training set and a test set. We have trained RESOLVED2 to predict FDA-aFS using a Cox model penalized by Lasso with cross validation on the training set. A cut-off probability was identified from the minimal log-rank derived p-value in the training set.

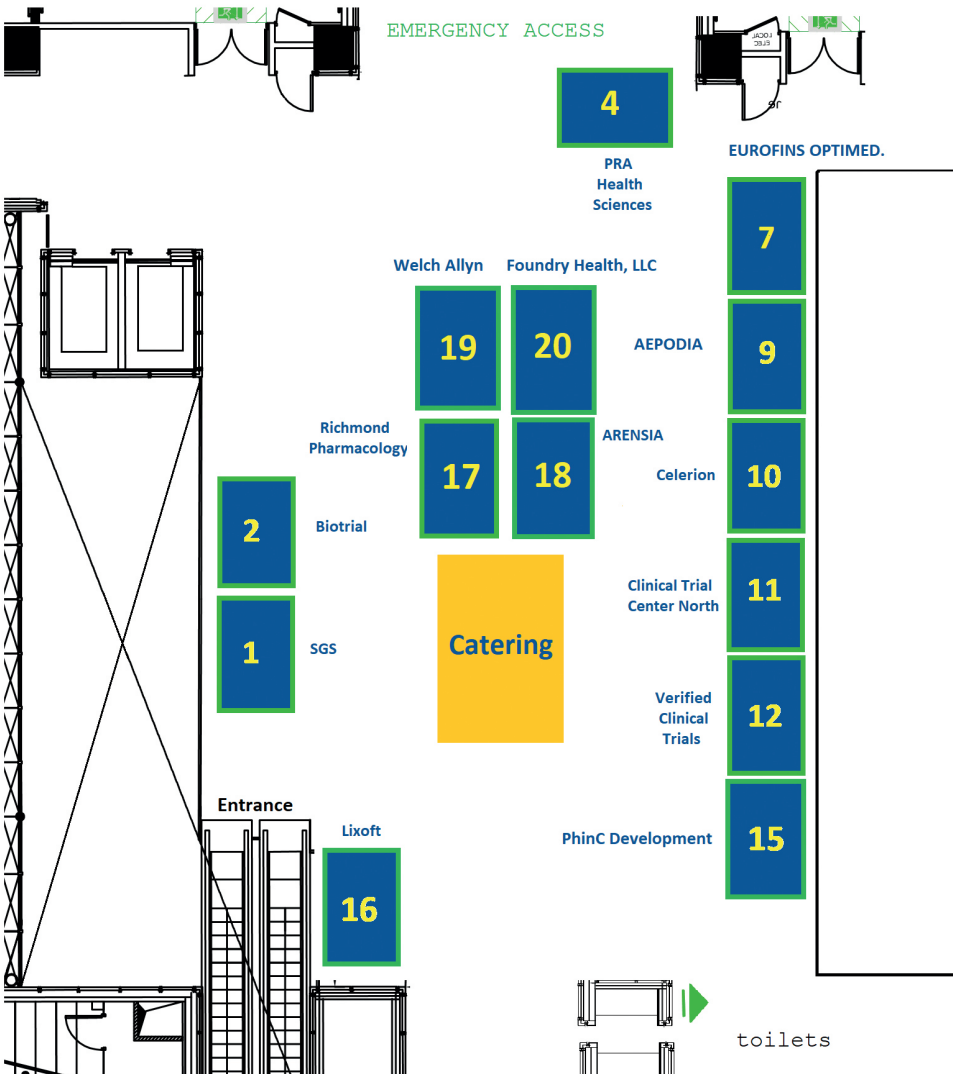
There were 462 ANA matching with DrugBank entries (P1CT publication interval: 1972-2017). Among 1415 variables, 29 remained in the model after Lasso penalization.

In the test set, the relation of the model to the FDA-aFS had a weighted concordance index of 0.91. Predicted class of approved treatements was highly related to observations in the test set: at 6 years of follow-up, 71% (95%CI [46%; 84%]) of predicted approved drugs were indeed approved and 92% (95%CI [87%; 98%]) of predicted non-approved drugs were still not approved (Hazard ratio=16.6; 95%CI [8.32; 33.2]; p<10e-10).

RESOLVED2 could support early go/no-go decision as soon as P1CT completion.

AUTHOR INDEX
SUBMITTED ABSTRACTS

EXHIBITION FLOORPLAN



*Floorplan not to scale. floorplan may be subject to change at the discretion of the organisers

Exhibitors	Position
SGS	1
Biotrial	2
PRA Health Sciences	4
EUROFINS OPTIMED.	7
AEPODIA	9
Celerion	10
Clinical Trial Centre North (CTC North GmbH & Co. KG)	11
Verified Clinical Trials	12
Lixoft	16
PhinC Development	15
Richmond Pharmacology	17
ARENSIA Exploratory Medicine	18
Welch Allyn	19
Foundry Health, LLC	20

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