FACULTY & ORGANISATION

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amcure GmbH	Karlsruhe (Germany)
Dr. Pawel Dobrzanski	
OncoArendi Theraputics SA	Warsaw (Poland)
Dr. Nicolas Frances	
F. Hoffmann-La Roche AG	Basel (Switzerland)
Dr. Heidi Kletzl	
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Dr. Thierry Lavé	
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REGISTRATION

CSi Hamburg GmbH
Goernestraße 30 · 20249 Hamburg (Germany)
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Attendance Fee
680 € Non Member
430 € Member of AGAH, EUFEMED or one of the VKliPha Societies

Registration form (Download PDF)

Registration Deadline: January 4, 2019
Due to a limited number of participants, confirmations will be on a ‚first come first serve' basis.

The participation fee is per person. Please note, according to §4 (22) German turnover tax law, workshop fees are exempt from VAT. Registration fees are charged and collected on behalf of the Organiser AGAH e. V. All bookings are subject to change.

CONTENT

INTRODUCTION
Selecting the adequate starting dose and defining appropriate dose escalation schemes in early clinical trials? A real challenge! Therefore, this workshop has been developed to specifically address translational aspects from the non-clinical to the clinical phase allowing for unique and detailed insight in a highly interactive manner between participants. A team of experienced experts including from industry, CROs, regulatory authorities, ethical review committees and investigators has put together a program which is entirely based on real examples. These case studies will be discussed step-by-step on the grounds of the recently revised European Guideline on Strategies to Identify and Mitigate Risks for First-In-Human and Early Clinical Trials with Investigational Medicinal Products.

Each case study will be presented and discussed to guide you through the following topics:

1. The non-clinical basis, including Pharmacology, DMPK and Toxicology
2. Translational modelling from non-clinical to clinical studies
3. And finally, the integration of the clinical outcome: reality check and refinement/lessons learned – has it worked?

This workshop will provide an excellent opportunity to foster a broader understanding of translational approaches and is designed for participants from regulatory agencies, industry, ethical review committees, academia and for investigators.

Over the last years, AGAH has been organising as series of workshops and discussion forums to address the events in Rennes and to contribute to the revision of the European FIH guideline. This upcoming workshop is in line with these earlier activities. It will focus on how to implement translational approaches from a practical perspective to design early clinical trials and to assess their adequacy and significance.

ORGANISER

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WORKSHOP VENUE

Hilton Hotel
Berliner Freiheit 2
53111 Bonn (Germany)

Accommodation at the workshop venue can be booked separately by the registration form.

Program subject to modifications status January 2019

AGAH
Arbeitsgemeinschaft für angewandte Humanpharmakologie e.V.
Association for Applied Human Pharmacology

AGAH WORKSHOP

ON THE IMPLEMENTATION OF TRANSLATIONAL APPROACHES TO SUPPORT DOSE SELECTION AND DOSE ESCALATION SCHEMES IN EARLY CLINICAL TRIALS

Program

JANUARY 24-25, 2019
BONN (GERMANY)

PROGRAM · DAY 1 · January 24, 2019 (Thursday)

09:00 Registration

10:00 **Welcome and introduction**
Stephanie Plassmann

10:15 **Revision of the FIH and early clinical trial guideline**
Elke Stahl
- Introduction of concept of uncertainty and exposure
- Maximum dose (exposure selection)
- Early clinical trials including integrated protocols

SESSION 1 NON-CLINICAL-BASIS
Chairs: Lutz Müller, Stephanie Plassmann

10:45 **Case Study no. 1:**
Risdiplam: Editing on the RNA level – a dream or a nightmare? – Spinal Muscular Atrophy as example
Lutz Müller
- Splice modification: biology - a new avenue for targeting diseases?
- The pharmacology hypothesis: in vitro patient cells or transgenic mouse?
- Lack of animal responder species for toxicology testing: how to validate, how to assess safety?
- Translation and management of adverse effects in animals - margin approach for healthy volunteers
- Safety translation for babies

Questions, Answers and Discussion

11:30 **Case Study no. 2**
Do we need to know the mechanism of action: the pitfalls and rewards of targeting chitinases
Pawel Dobrzanski
- Chitinases: novel therapeutic targets for inflammatory and fibrotic diseases
- Developing chitinase inhibitors and developing the science: how to adjust to evolving rationale
- Building the case for a clinical candidate without a clear mechanism of action

Questions, Answers and Discussion

12:15 Break

13:15 **Case Study no. 3 AMC303: Non-clinical characterisation of a peptide based CD44v6 inhibitor in cancer therapy**
Klaus Dembowsky
- Peptide based approach to target one highly specific RTK co-receptor, CD44v6
- First in class inhibitors with significantly improved specificity and different mode of action
- Downstream blockade of several oncological pathways (VEGF/VEGFR-2, HGF/c-Met and MSP/RON) rather than currently available treatment options that target only one receptor tyrosine kinase e.g. VEGFR or one growth factor e.g. VEGF
- CD44v6 inhibition results in inhibition of tumour growth, the development and regression of metastases: pharmacological characterization
- Tumour specific target expression – predictivity of non-clinical safety studies to support risk assessment, dose selection and monitoring for FIH studies in cancer patients

Questions, Answers and Discussion

PROGRAM · DAY 1 · January 24, 2019 (Thursday)

14:00 **Round table discussion**
"The Good, the Bad and the Ugly" and how to deal with them
All Workshop participants

14:30 Break

SESSION 2 TRANSLATIONAL MODELLING
Chairs: Elke Stahl, Özkan Yalkinoglu

15:00 **Case Study no. 1: Risdiplam: Targeting a clinical dose from pre-clinical data: a playbook**
Nicolas Frances
- Working RNA splice data into a model
- How much splice change, how much protein?
- What is the maximal effect – on RNA, on protein?
- Modelling for babies

Questions, Answers and Discussion

15:45 **Case Study no 2: Chitinase inhibitor: from candidate ID to clinical dose selection**
Stanislaw Pikul
- Animal models versus human disease
- PK/PD relationships
- Toxicology program

Questions, Answers and Discussion

16:30 **Case Study no 3: AMC303: PK/PD modelling for selection of starting dose and escalation schemes**
Klaus Dembowsky
- Challenges associated with specificity: how to predict human dose in cancer patients based on safety studies in healthy animals and on preclinical pharmacology
- Essentials of the non-clinical characterisation
- Translational modelling to predict human doses

Questions, Answers and Discussion

17:15 **Round table discussion**
Translational modelling: a black box or the holy grail to unravel the mystery?
All Workshop participants

17:45 **End of Day 1**
GET-TOGETHER

PROGRAM · DAY 2 · January 25, 2019 (Friday)

SESSION 3: CLINICAL OUTCOME
Chairs: Gerd Mikus, Barbara Schug

09:30 **Key considerations regarding dose escalation schemes in FIH and early clinical trials**
Thomas Sudhop

09:50 **Case Study no 1: Risdiplam: Prediction from bench to bedside – how a vision translates into reality in HV and patients**
Heidi Kletzl
- Clinical pharmacokinetics and pharmacodynamics
- Dose and exposure
- RNA and protein
- Adolescents and babies
- Maximal effect?

Questions, Answers and Discussion

10:35 **Case Study no 2: First human experience with the chitinase inhibitor**
Stanislaw Pikul
- Human PK modeling
- Clinical Phase I design
- Challenges with selection of therapeutic dose

Questions, Answers and Discussion

11:20 **Case Study no 3: AMC303: How did target expression and biomarker predict clinical outcome? How do preclinical data correlate with clinical data?**
Klaus Dembowsky
- Presentation of clinical Phase I/Ib trial design
- Topline results from the dose escalation part and outcome of data safety monitoring board
- Clinical pharmacokinetics and biomarker
- Dose and exposure
- Patients
- Initiation of expansion cohort of ongoing phase I/Ib study

Questions, Answers and Discussion

12:05 Break

13:05 **Round table discussion**
"Reality check and refinement/lessons learned – has it worked? – Is a standardised approach adequate or were case by case plans more successful?"
All Workshop participants

14:00 **Closing remarks**
Barbara Schug

14:15 **Farewell**