Background: Classic clinical trial design (randomized double-blind comparison of parallel groups) is the gold standard for establishing efficacy of new treatments and is robust, credible, and easy to interpret. Limitations include a long experimental phase before any conclusion may be taken, lack of feasibility when requirements for sample size to achieve significance are higher than the available population, such as in rare diseases, and may be ethically questionable if already available information is ignored while the study is ongoing.
Results: Alternatives include a number of designs aimed to improve efficiency, flexible designs and adaptions, sequential methods, Bayesian-based approaches, or combinations, amongst others. Variations of the parallel design, such as challenge-dechallenge-rechallenge, crossover methods, or population enrichment, may improve efficiency in certain clinical circumstances. When the timing for end points is shorter than the recruitment period, sequential methods take advantage of information as it is gathered and allow to limit recruitment to that strictly necessary to reach conclusions; improvements in real-time data collection and validation have removed obstacles to applicability of these long-time described methods. Adaptions are pre-specified modifications of the trial design during study execution in a number of likely scenarios. Uncertainty in key features of the study design, including the expected efficacy of the tested products, variability of measures, or rates of response, may be managed by using adaptive approaches. Bayesian designs use both the prior information and the information obtained in the study to synthesize accumulated evidence. Biological and statistical modelling allow refinement of designs.
Conclusions: Alternative methods should not be means of relaxing requirements, but tools to improve efficiency. Study a priorism and operational integrity should be ensured, especially when interim inspections are made and early decisions are taken; statistical efficiency should never preclude that clinically relevant and interpretable results are obtained.

1.8

CURRENT CHALLENGES AND HURDLES IN NEW DRUG DEVELOPMENT

S. Vukicevic
Center for Translational and Clinical Research, School of Medicine, University of Zagreb, Zagreb, Croatia

New drugs in the last 60 years extended the longevity for 10 years by an average of two months each year. Although investment in pharmaceutical R&D dramatically increased over the last 60 years, the number of new approved drugs remains low. So far FDA approved more than 1340 new drugs out of which around 1150 are small molecules and 190 are biologicals. Around 50 billion dollars are invested in R&D per year. Annually FDA approves approximately 20-25 new drugs; for example, in 2010 FDA approved 21 new drugs and the probability that a company's new medical entity (NME) output will exceed 2 or 3 per year is 0.06% and 0.003%, suggesting that NME output cannot reach the threshold of sustainability. The price of individual preclinical and clinical drug development exceeds 1.5 billion dollars; however, recently large companies reported costs between 3.7 to 12 billion dollars for newly approved oncology drugs. The current business model is therefore considered unsustainable and below the level required to secure the future of pharmaceutical industry. Interestingly, the constant rate of drug discovery is not influenced by technology, mergers, acquisitions and other non-scientific interventions. New approaches that engage small companies, governments, and academic organizations are developing. The limitations of the current R&D and new options to achieve sustained drug development will be discussed.

1.9

HOW TO PROMOTE CLINICAL RESEARCH IN CEE?

R. Spaventi
Triadelta Partners Ltd., Zagreb, Croatia

Central and Eastern Europe is a region with a number of competitive advantages for successful performance of clinical trials. These advantages include highly motivated investigators, centralized health care systems, good infrastructure, treatment-naive patients, well educated and trained professionals in local clinical CROs, overall favourable cost structure, etc. However, in spite of its unquestionable potential, the number of clinical trials in most of the countries from the region are markedly falling below Europe's average. The lecture will elaborate on potential roots of this situation and propose potential measures that could catalyse utilization of full potential of the region.

1.10

MEDICINAL PRODUCT REGULATION: PORTUGAL'S FRAMEWORK

M.T. Herdeiro[1,2,3,4]; P.A. Dias Bastos[1,2,3,4]; A. Teixeira Rodrigues[1,2,3,4]; and F. Roque[1,2,3,4]
[1]Department of Medical Sciences and Institute for Biomedicine – iBiMED, University of Aveiro, Aveiro, Portugal; [2]CESPU, IINFACTS, Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, Gandra, Portugal; [3]Division of Biochemistry, Chemistry Department, University of Aveiro, Aveiro, Portugal; and [4]Research Unit for Inland Development, Guarda Polytechnic (UDI/IPG), Guarda, Portugal

Introduction: The prescription, supply and use of medicines should centre on their rational use, in order to foster patients' interests and integrity, and promote public health and national economic sustainability. The pharmaceutical industry is one of the most tightly regulated sectors, and it is essential to know each country's legislative framework in order to understand the regulation, approval, and marketing of medicinal products for human use. Portugal has played an important role in the European Union and European Economic Area as a Reference Member State (RMS). The aim is to describe the main statutes and procedures governing medicinal products for human use in Portugal, as well as the role of the country's National Medicines and Health Products Authority.
Methods: Data were sourced from the INFARMED website, Infomed database of medicinal products for human use, and periodic reports issued by national authorities.
Results: During Portugal's term as RMS, the number of marketing authorisations has risen, and in 2015 Portugal ranked 5th in the European System of Medicines Evaluation in terms of the number of completed procedures as RMS. Close to 80% of all approved drug applications in Portugal in 2015 were for generic drugs, mostly pertaining to the nervous system. The Portuguese market for medicinal products for human use has been appreciably changed by the advent of generic drugs, and the most urgent need in Portugal appears to correspond to the nervous system. Furthermore, a large proportion of all available human medicines is subject to reimbursement. Portugal has assumed increasing importance as a reference state for the approval of new human medicines and might become an important country for conducting phase III trials of immunomodulatory drugs.
Conclusions: There is an increase trend for new request application for biological and biotechnological substances.
Acknowledgment: The authors would like to thank Foundation for Science and Technology (PTDC/SAUESA/105530/2008) and iBiMED (UID/BIM/04501/2013).

1.11

INCONSISTENCY IN PRECLINICAL AND CLINICAL TRIALS EXPLORING THE ROLE OF HORMONE REPLACEMENT THERAPY IN ALZHEIMER'S DISEASE

J. Osmanovic-Barilar; and M. Salkovic-Petrisic
University of Zagreb School of Medicine, Zagreb, Croatia

Introduction: Hormone replacement therapy (HRT) is widely prescribed in women during or after menopausal transition to replace decline in estrogen (E) and progesterone (P4) level. While some studies indicate that E and P4 depletion in postmenopausal women might carry a significant risk for developing sporadic Alzheimer's disease (sAD), which may be reduced by E-based HRT, recent clinical trials oppose the beneficial effect of such therapy. We aimed to explore possible reasons for such inconsistency in preclinical and clinical trials on HRT in AD condition.

Methods: PUBMED database (reviews, meta-analysis, and original papers) was searched (1994-2016) by using the following keywords: HRT, E, P4, AD, menopause, and cognition.

Results: An overview of literature search revealed that possible reasons for such inconsistency can be found both in preclinical and clinical trials as well as in the HRT itself, roughly classified as follows:

1. Inappropriate animal models that result in incorrect translation of animal-to-human or human-to-animal condition regarding the type of sex hormone depletion (abrupt/surgical removal of gonads or gradual/physiological exhaustion of gonads) and regarding the AD form (widely exploited transgenic models represent rare familiar but not prevailing sAD form)
2. Heterogeneous postmenopausal women groups in clinical trials (regarding the sAD stage or anti-AD and concomitant drug therapy and hysterectomy status)
3. Incomparable HRT treatment design in/within preclinical and clinical trials (different estrogen/progestogen compounds and dose, route of administration, pharmaceutical formulation, and timing of treatment initiation)

Conclusion: To answer the question on possible beneficial effect of HRT in postmenopausal women with sAD, further research is needed both in humans and animals that will take all mentioned issues into account and additionally focus on other types of estrogen and progestogen compounds, including progestins like norprogesterones, levonorgestrel, and selective modulators of estrogen receptors.

1.12

THE EFFECTS OF SENS-111, A NEW H4R ANTAGONIST, ON VERTIGO INDUCED BY CALORIC TEST IN HEALTHY VOLUNTEERS (HV) IS RELATED TO PLASMA CONCENTRATIONS

P. Attali[1,2,3,4]; R. Gomeni[1,2,3,4]; E. Wersinger[1,2,3,4]; S. Poli[1,2,3,4]; and F. Venail[1,2,3,4]
[1]Sensorion, Montpellier, France; [2]Pharmacometrica, La Fouillade, France; [3]Consultant in Pharmacokinetics, Geneva, Switzerland; and [4]Hopital Gui de Chaulliac, Montpellier, France

Background: SENS-111, a new selective nonsedative H4R antagonist, was reported to reduce vertigo induced by a caloric irrigation in HV. However, no optimal daily dose from 50 to 250 mg/d for 4-7 days could be identified due to the large inter- and intra-variability of symptoms induced by the caloric irrigation. The relationship between PK parameters and the effects on vestibular symptoms was thus investigated.

Methods: Five cohorts of 12 HV were given either a capsule of SENS-111 (9 subjects/cohort) or placebo (3 subjects) orally once daily for 4 days (50, 100, 150 mg/d) or 7 days (200 and 250 mg/d) according to a randomized double-blind dose escalating design. Following 3 baseline recordings at 3h interval before treatment, nystagmus (latency, duration, frequency) and vertigo symptoms were evaluated daily 2 hours post dosing using video nystagmography, questionnaires (latency, duration of appearance/disappearance), Visual Analog Scale (intensity), and European Evaluation Vertigo Scale. A population PK analysis was conducted on all data collected in the study. Then, two descriptive PK/PD analyses were conducted on the change from baseline values considering the SENS-111 exposure up to 500 ng/mL and up to 1000 ng/mL. Finally, a model based approach was developed to account for the individual trajectories of the response.

Results: The latency of vertigo appearance increased with exposure at concentrations below 500 ng/mL ($p=0.0367$) while it decreased with concentrations ranging from 500 to 1000 ng/mL. Similarly, the duration of vertigo decreased with the increase of exposure ($p=0.0455$) at concentrations below 500 ng/mL while it increased with the exposure at concentration above 500 ng/mL. Data on other end points will also be presented.

Conclusions: Vertigo end points were improved by SENS-111 up to concentrations of 500 ng/mL and then progressively deteriorated. This is consistent with preclinical findings and may be related to off-target effects at high concentrations.

1.13

ARE WE SCARED OF CLINICAL TRIALS IF NOT SUFFICIENTLY INFORMED AND EDUCATED?

L. Burnazovic-Ristic; M. Rakanovic-Todic; S. Maleskic; A. Kulo Cesic; and J. Kusturica
Medical Faculty University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Introduction: Clinical trials (CTs) are prospective biomedical research studies designed to answer specific questions about new treatments and already known interventions. Clinical trials are highly regulated by highest authorities and mainly generate data on safety and efficacy. Previous studies identified main barriers to participation in CTs as concerns of patients about provided information, safety, and costs. Usually medical curricula are not directed for wider education in this topic, but basic information is shared within several subjects. In this study we explored the basic knowledge and attitude about clinical trials among medical students, having in mind their further involvement in performing of trials as well as educating the community raising awareness about participation.

Material and Methods: This study was designed as a cross-sectional, self-report online survey among medical students of Medical Faculty University of Sarajevo.

Results: Among 142 students who completed questionnaire, 72.5% did not respond to a question about their own satisfaction with the knowledge about CTs. Majority of the students were unfamiliar with awareness of conducting international clinical trials in Bosnia and Herzegovina (71.8%) and getting transparent information on a web page of Regulatory Drug Agency (80%). They had an overall positive attitude toward importance of CTs in education of health professionals with 85% of answers with sub-maximum and maximum score. However, only 38% would participate in a CT.

Conclusions: Overall, the medical students showed insufficient knowledge and lack of awareness about CTs. Similar findings are described in literature as major barriers to recruitment and enrolment of patients. Specific areas of deficient knowledge are recognized, and these results could be useful as a general guidance for curriculum