II (lixislamente, saxagliptin), depression (amoxetine), bipolar disorder (asenapine), and epilepsy (eslicarbazepine). Data of all Phase II and III trials were identified in the European public assessment reports, the WHO Trials Registry, and PubMed. Outcome measures: the number of randomized subjects and the number of those aged 65 and 75 years and older. Trials with missing data were not included in the calculation of that outcome. Rates of trials giving information about the number of older subjects and the proportions of older people were calculated.

Results: The number of people aged 65+ and 75+ was available in 39% and 48% of the 116 included trials, respectively. The proportion of older people varied from 0% to 93%. In trials for indications primarily related to aging (n = 7), 47.1% of the subjects were 65+ (median, 2681; range, 524–5848); 20.6% were 75+ (median, 1575; range, 216–5848). In trials for indications not specific for, but present in old age (n = 5), 7.5% of the subjects were 65+ (median, 108; range, 14–887); 0.9% were aged 75 and older (median, 26; range, 0–83).

Conclusion: This study on the number of older subjects in clinical trials of recently authorized drugs shows that in trials for indications primarily related to aging, almost half of the randomized subjects are aged 65 and older. In trials for indications not specific for, but present in old age, the number and especially the proportion of older subjects is limited. So, serious improvement concerning the inclusion of the older target population is needed for drugs intended for younger as well as for older patients.

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OC020—OPTIMAL SAMPLING STRATEGY FOR BUSULFAN IN STEM CELL TRANSPLANTATION PATIENTS

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Introduction: Busulfan, an alkylating agent, is used in combination with other drugs in patients undergoing stem cell transplantation. Busulfan presents a very narrow therapeutic window, which has been linked to various adverse events. Therapeutic monitoring protocols have been developed to allow the individualization of the dose, but the dose selection and the sampling time for pharmacokinetics are based on empirical evidence. Consequently, target exposure cannot be warranted. The aim of this investigation was to determine the optimal sampling scheme and develop a model-based dosing algorithm for busulfan in stem cell transplantation patients.

Patients (or Materials) and Methods: Clinical data (n = 29) from an ongoing study were used for the purposes of our analysis. A 1-compartment model was selected as basis for sampling optimization and subsequent evaluation of a suitable dosing algorithm. Internal and external model validation procedures were performed before the optimization steps using ED-optimality criteria. Clearance and volume of distribution were considered as parameters of interest. The final sampling scheme and dosing algorithm were based on the deviation from target exposure range, as determined by AUCref

Results: A 1-compartment model was found to describe busulfan exposure after oral administration, with ideal body weight (IBW) and alanine transferase (ALT) as covariates on clearance. Microautoradiographic localization in the respiratory tissues was evaluated after a single intranasal administration of radiolabeled LO to mice. In addition, the disposition of LO and laninamivir was evaluated by measuring the drug uptake and release in primary cultured mouse airway epithelial cells.

Results: In healthy volunteers, the peak plasma concentrations of laninamivir occurred at 3.5 hours after inhalation and decreased with the half-life of 45.7 hours. Laninamivir concentrations in ELF and AM were much higher than those in plasma and lasted for 240 hours. \( C_{\text{peak}} \) of laninamivir in ELF from first BAL was 8.6 μg/mL and laninamivir in ELF decreased with longer half-life (~6 days) than in plasma. Laninamivir concentrations in ELF notably exceeded the IS0 values for viral neuraminidase at all time points examined. In mice, the labeled LO derived activity after an intranasal administration mainly located on the epithelial cells for a long period. The uptake of LO in airway epithelial cells increased without any apparent saturation even at the highest concentration tested (1000 μM). Furthermore, the intracellular laninamivir was released very slowly into the drug-free medium, which was regarded as a rate-limiting step in the cellular retention.

Conclusion: ELF concentration profiles and prolonged high intrapulmonary retention of laninamivir support its long-lasting efficacy to treat patients with influenza virus infection by the single inhalation.


OC019—INTRAPULMONARY PHARMACOKINETICS (PK) AND THE INTRACELLULAR DISPOSITION TO SUPPORT THE LONG-LASTING EFFICACY AFTER AN INHALED ADMINISTRATION OF ITS PRODRUG LANINAMIVIR OCTANOOATE (LO)

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Introduction: A single inhaled dose of laninamivir octanoate (LO), a long-acting neuraminidase inhibitor, exhibits efficacy to treat both adult and pediatric patients with influenza virus infection. However, the relation between the intrapulmonary pharmacokinetics (PK) of LO and laninamivir, an active metabolite, and its long-lasting efficacy has not fully been investigated. Intrapulmonary pharmacokinetics in healthy volunteers and the intracellular drug disposition in mice were evaluated to clarify the potential mechanism for the prolonged high intrapulmonary retention of laninamivir, which would support its long-lasting efficacy.

Patients (or Materials) and Methods: A single-center, open-label study was performed in adult healthy volunteers. Seven subgroups of 5 subjects each underwent bronchoalveolar lavage (BAL) at specified time intervals from 4 to 240 hours after a single inhaled administration of LO (40 mg). Plasma, BAL, fluid, and alveolar macrophage (AM) were analyzed to determine laninamivir and LO concentrations using validated LC-MS/MS methods. The concentrations in epithelial lining fluid (ELF) were calculated by the urea diffusion method. Microautoradiographic localization in the respiratory tissues was evaluated after a single intranasal administration of radiolabeled LO to mice. In addition, the disposition of LO and laninamivir was evaluated by measuring the drug uptake and release in primary cultured mouse airway epithelial cells.

Results: In healthy volunteers, the peak plasma concentrations of laninamivir occurred at 3.5 hours after inhalation and decreased with the half-life of 45.7 hours. Laninamivir concentrations in ELF and AM were much higher than those in plasma and lasted for 240 hours. \( C_{\text{peak}} \) of laninamivir in ELF from first BAL was 8.6 μg/mL and laninamivir in ELF decreased with longer half-life (~6 days) than in plasma. Laninamivir concentrations in ELF notably exceeded the IS0 values for viral neuraminidase at all time points examined. In mice, the labeled LO derived activity after an intranasal administration mainly located on the epithelial cells for a long period. The uptake of LO in airway epithelial cells increased without any apparent saturation even at the highest concentration tested (1000 μM). Furthermore, the intracellular laninamivir was released very slowly into the drug-free medium, which was regarded as a rate-limiting step in the cellular retention.

Conclusion: ELF concentration profiles and prolonged high intrapulmonary retention of laninamivir support its long-lasting efficacy to treat patients with influenza virus infection by the single inhalation.


OC020—OPTIMAL SAMPLING STRATEGY FOR BUSULFAN IN STEM CELL TRANSPLANTATION PATIENTS

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Introduction: Busulfan, an alkylating agent, is used in combination with other drugs in patients undergoing stem cell transplantation. Busulfan presents a very narrow therapeutic window, which has been linked to various adverse events. Therapeutic monitoring protocols have been developed to allow the individualization of the dose, but the dose selection and the sampling time for pharmacokinetics are based on empirical evidence. Consequently, target exposure cannot be warranted. The aim of this investigation was to determine the optimal sampling scheme and develop a model-based dosing algorithm for busulfan in stem cell transplantation patients.

Patients (or Materials) and Methods: Clinical data (n = 29) from an ongoing study were used for the purposes of our analysis. A 1-compartment model was selected as basis for sampling optimization and subsequent evaluation of a suitable dosing algorithm. Internal and external model validation procedures were performed before the optimization steps using ED-optimality criteria. Clearance and volume of distribution were considered as parameters of interest. The final sampling scheme and dosing algorithm were based on the deviation from target exposure range, as determined by AUCref

Results: A 1-compartment model was found to describe busulfan exposure after oral administration, with ideal body weight (IBW) and alanine transferase (ALT) as covariates on clearance. A sparse sampling scheme with five samples per patient (t = 0.5, 2.25, 3.4, and 5 hours after dose) was found to be sufficient for the characterization...
of busulfan pharmacokinetics. In conjunction with sparse sampling, the proposed model-based dosing algorithm appears to ensure that patients achieve and maintain the expected target exposure.

Conclusion: In contrast to the current clinical protocol, which relies on a linear correlation between dose and body weight, our findings reveal the clinical implications of a nonlinear correlation between body size, liver function, and drug elimination. The definition of the sparse ideal optimal design for busulfan constitutes an important improvement in therapeutic drug monitoring routine. Moreover, the availability of a model-based dosing algorithm for dose individualization may contribute to considerable improvement in the safety and efficacy profile of patients undergoing treatment for stem cell transplantation.

Disclosure of Interest: None declared.

OC021—CLINICAL TRIALS REGISTRY AND GOOD CLINICAL PRACTICE: IN INDIAN SCENARIO
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Introduction: In present scenario, India becomes a hub for conducting clinical trials. Hence, need good clinical practice (GCP) to conduct a clinical trial. Initiative of Indian government of clinical trial registry (CTRI) has helped in increasing transparency, accountability, and accessibility of clinical trials. We conducted retrospective observational study aimed to establish current Indian status of Good Clinical Practice certified clinical investigators in major government hospitals, private hospitals, and small polyclinic.

Patients (or Materials) and Methods: We have done extensive search of clinical trials registry in India to obtain information regarding the total number of trials registered and further divided into the sites specific like major government hospitals, private hospitals, and small polyclinic from year 2007 to 2012.

Results: Our paper is first of a kind to demonstrate the sites preferred by sponsor or investigator for conducting clinical trials. Looking into the data, it was found private institutes were preferred compared with government institutes and increasing number of trials were also conducted in polyclinics. Trends toward allocating of private institute though increased by 2011 but by 2012, both government and private institutes were equally allocated for clinical trials but decrease in registration of trials is noticed by the 2012. Proper coordination and timely completion of trial should be aimed at properly trained, qualified, and experienced staff (GCP trained) with standard laboratories and regular monitoring.

Conclusion: Present study showed the importance and differences of site specific application of GCP objectives. The principle of GCP should be followed regardless of site and then expect a good clinical outcome and training during the study.

Disclosure of Interest: None declared.

OC022—INTERCHANGEABILITY OF GABAPENTIN GENERIC FORMULATIONS IN THE NETHERLANDS: A COMPARATIVE BIOAVAILABILITY STUDY
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Introduction: This study (in vivo) was performed to investigate so-called “drift” with generic-generic drug substitution, namely whether a registered generic formulation is also bioequivalent to another generic formulation, fulfilling the 80% to 125% criterion.

Patients (or Materials) and Methods: This bioequivalence study was conducted at Maastricht University Medical Centre, and designed as a 800-mg tablet, single-dose, 4-treatment (Neurontin® and 3 registered generic gabapentin products), randomized, 4-way crossover trial in 24 healthy volunteers under fasting conditions.

Results: Six comparisons were performed among the 4 treatments to investigate the bioequivalence of different gabapentin formulations. In all comparisons, the 90% CIs for the reference/test ratio of Cmax, AUC0–24, and AUC∞ were within the routine 80.00% to 125.00% criterion. The safety and tolerability profiles were comparable.

Conclusion: In this comparative bioavailability study, all 3 generic formulations of gabapentin were found to be interchangeable with Neurontin® and were also shown to be bioequivalent to each other. These results indicate the absence of a “drifting” problem upon gabapentin generic-generic exchange. Our study results are in line with those obtained from a previously conducted simulation study with topiramate and gabapentin based on bioequivalence data present in the registration files of the Dutch Medicines Evaluation Board. Compared with the simulation study for generic-generic interchange, the ratios in the currently reported comparative bioavailability study are comparable, albeit with narrower 90% CIs for Cmax and AUC.

Disclosure of Interest: None declared.

Reference

OC023—DO TREATMENT QUALITY INDICATORS PREDICT CARDIOVASCULAR OUTCOMES IN PATIENTS WITH DIABETES?
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Introduction: Landmark clinical trials have led to optimal treatment recommendations for patients with diabetes. However, whether optimal treatment is actually delivered in practice is more important than the efficacy of the drugs tested in trials. To this end, treatment quality indicators have been developed and tested against intermediate outcomes of cardiovascular complications. No studies have tested whether these treatment quality indicators also predict hard patient outcomes.

Patients (or Materials) and Methods: Data were collected from 10,056 patients with diabetes in the Groningen Initiative to Analyze Type 2 Treatment (GIANTT) database and Dutch Hospital Data register. Included quality indicators measured glucose, lipid, blood pressure, and albuminuria-lowering treatment status and treatment intensification when indicated. Hard patient outcome was the composite of cardiovascular events and all-cause death. Associations