duodenogastric reflux (PDGR) with high-amplitude changes in gastric pH can lead to destruction of the coating layer, resulting in degradation of the active compounds due to decrease in pH level after a reflux. The pH increasing ≥4 within PPIs administration also promotes dissolution of poor-quality coating.

Methods: Modified comparative dissolution testing of original omeprazole (OO) and Generics1;2;3;4 proceeded in two stages. At first, we moved drugs from solution with Ph=1.2 (1.2 ± 0.05) to pH=7.0 (7.0 ± 0.05) and examined concentration of omeprazole in solution using high-performance liquid chromatography (HPLC). According to our self-developed formula, pH 7 exposure time of resistance to PDGR for omeprazole is 4 minutes, i.e. the active substance should not be released within 4 minutes at pH 7. The exposure at the second stage was conducted with pH 4 (4.0 ± 0.05), which imitated gastric pH after PPI administration. And then we also moved drugs to pH 7 with the subsequent measurement of omeprazole concentration.

Results: Omeprazole concentrations after 4, 10, 15, 20, 30, 45, 60 minutes in pH 7 solution at the first stage (pH 1.2 exposure) were different for OO and generics. For OO, these values were 4,7 ± 0,7%; 41,4 ± 3,0%; 62,8 ± 4,0%; 79,5 ± 2,9%; 83,5 ± 2,9%; 81,6 ± 2,9% (partly degradation of omeprazole); 80,6 ± 4,4%; for Generic1 - 0; 49,3 ± 9,9%; 88,8 ± 2,8%; 90,4 ± 3,7%; 88, 2 ± 2,2%; 87,3 ± 2,0%; 85,9 ± 1,1%; for Generic2 - 0; 30, 6 ± 6,3%; 66,7 ± 8,2%; 76,4 ± 7,4%; 82,8 ± 5,3%; 86,0 ± 3,7%; 84,6 ± 3,3%: for Generic3 - 80,8 ± 3,6%; 83,5 ± 1,9%; 83, 8 ± 3,2%; 83,3 ± 2,7%; 81,9 ± 2,1%; 82,1 ± 2,0%; 82,0 ± 2,4%; for Generic4 - 82,5 ± 1,7%; 84,4 ± 0,8%; 84,2 ± 1,2%; 82, 9 ± 0,9%; 82,9 ± 0,9%; 82,9 ± 0,9%; 82,8 ± 1,1%, respectively.

An analysis of the omeprazole concentration in pH 7 solution at the second stage (pH 4 exposure) revealed the following parameters after 4, 10, 15, 20, 30, 45, 60 minutes: for OO - 4,4 ± 0,6%; 40, 5 ± 3,0%; 62,8 ± 2,0%; 80,0 ± 3,1%; 85,4 ± 2,9%; 82,8 ± 3,4%; 80,9 ± 3,5%; for Generic1 – 0; 67,0 ± 7,8%; 89,7 ± 2,3%; 91, 9 ± 4,3%; 89,1 ± 1,6%; 88,3 ± 1,4%; 87,8 ± 1,2%; for Generic2 – 0; 42,2 ± 5,6%; 75,1 ± 7,3%; 81,0 ± 6,0%; 88,4 ± 3,2%; 88, 6 ± 1,3%; 87,9 ± 1,0%; for Generic4 – 85,5 ± 0,5%; 85,6 ± 0,5%; 84,7 ± 0,9%; 82,7 ± 3,0%; 84,4 ± 0,3%; 84,4 ± 0,3%; 84,3 ± 0,4%, respectively. Generic3 release and degradation were completely realized at pH 4.

Conclusion: Gastric stability of Generic3 and Generic4 has been decreasing due to PDGR and pharmacodynamic effect of the PPIs themselves.

THREE-YEAR CONTRIBUTION OF ECRIN (EUROPEAN CLINICAL RESEARCH INFRAESTRUCTURE NETWORK) TO THE SUPPORT OF ACADEMIC MULTINATIONAL CLINICAL RESEARCH

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Background: ECRIN is a pan-European distributed infrastructure dedicated to fostering competitiveness of academic multinational clinical research across Europe, with high ethical and scientific standards. This target is achieved by the interaction, interoperability and harmonized work between European countries and their respective National Clinical Research Networks with the coordinated support of ECRIN-ERIC.

Objectives: To describe the role of ECRIN in the support of academic clinical research during the last three years, considering publicly-funded multinational clinical research projects and structuring activities.

Methods: Descriptive analysis, considering the number and type of projects and the clinical area involved.

Results: The activity of ECRIN has been developed in three main courses of action:

Courses of action	Scientific and logistical support to publicly-funded multinational clinical research projects	Structuring projects	Evaluation of capacity and scientific impact
Number of proposals and projects	Support to 49 proposals Support to 11 H2020 funded projects	9 active structuring projects	–1 capacity building survey –1 analysis of quality and scientific impact
Thematic approach	Drug repurposing, comparative effectiveness, rare diseases, chronic diseases, cohorts and patient stratification	– Certification programme of Clinical Trial Units – Coordinated actions with other research infrastructures – Development of international gold standards in clinical research – Training of clinical research networks – Doctoral programmes	Analysis of: Structure capacity Impact of clinical research and its scientific support to National Health Systems
Clinical areas	Cardiology, Neurology, Infectious diseases, Liver diseases, advanced therapies, Orthopedic surgery, Pneumology	Integrative and transversal approach covering all clinical areas	Integrative and transversal approach covering all clinical areas

Conclusions: The activity of ECRIN has grown in a sustainable fashion during the last three years to include a wide range of supporting activities to academic clinical research, involving not only the coordination of multinational clinical research projects, but also structuring and quality assurance activities.

ASSESSMENT OF CYP2C19, ABCB1, CYP3A5 GENES POLYMORPHISMS' AND CYP3A4 ISOENZYME ACTIVITY INFLUENCE ON MAJOR ADVERSE CARDIOVASCULAR EVENTS AMONG PATIENTS WITH AN ACUTE CORONARY SYNDROME UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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Background: The aim of this study was to determine the impact of *CYP2C19, ABCB1, CYP3A5* genes polymorphisms and CYP3A4 isoenzyme activity on clopidogrel laboratory resistance and incidence of major adverse cardiovascular events (MACE) among patients with an acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

Methods: 76 patients (median age 63, range 37 to 91 years) with an ACS who underwent PCI were screened for *CYP2C19, ABCB1, CYP3A5* genes polymorphisms: *CYP2C19*2, CYP2C19*3, CYP2C19*17, ABCB1 C3435T, CYP3A5*3*. Allelic variants were detected by the method of real-time polymerase chain reaction. CYP3A4 isoenzyme activity was determined by urine cortisol and 6-beta-hydroxycortisol levels. Such MACE as stent thrombosis (n=2) and restenosis (n=1) were observed.

Results: Clopidogrel laboratory resistance (PRU>208) was found to be higher in the CYP2C19*2-carriers as compared to non-carriers: 53.8% vs 16.2% (OR=1.8; 95% CI: 1.0–3.2; p=0.0067). Higher risk of thrombosis was associated with low mean 6-beta-hydroxycortisol / cortisol ratio and, consequently, impaired CYP3A4 activity (β coefficient=0.022, SE 0.009, p=0.021 in the linear regression model). *CYP2C19*17*, *ABCB1 C3435T* and *CYP3A5*3* polymorphisms did not affect platelet reactivity. The presence of the *CYP2C19*2* polymorphism did not affect the incidence of stent thrombosis (β=-1.626, SE=1.449, p=0.262 in the logistic regression model), nor did the *CYP2C19*17* (β=-0.907, SE=1.438, p=0.528 in the logistic regression model) and *ABCB1 C3435T* polymorphisms (β=1.270, SE=1.442, p=0.378 in the logistic regression model). The *CYP3A5*3* polymorphism did not affect the incidence of stent thrombosis as well (β = -17.633, p=0.999 in the logistic regression model).
Conclusions: CYP2C19*2-carriership in ACS patients undergoing PCI significantly increases the risk of clopidogrel laboratory resistance. However we did not find evidence that the presence of *CYP2C19*2, CYP2C19*17, ABCB1 C3435T, CYP3A5*3* polymorphisms may jeopardize clinical effectiveness and safety of PCI in patients with an acute ACS. However, impaired CYP3A4 isoenzyme activity may increase the risk of stent thrombosis.

ASSESSMENT OF USE OF DRUGS AT ELDERLY WITH OUT-OF HOSPITAL PNEUMONIA

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One of the most important tasks of Clinical Pharmacology - strict adherence to the principles of Rational use of drugs in geriatrics to increase the efficiency and safety of pharmacotherapy.

The purpose of research - pharmacoepidemiology drugs in the elderly.
Study Design: -Retrospective pharmacoepidemiological. Analysis of medical history data 632 elderly patients with out-of hospital pneumonia. Assessment indicators: the interaction effect of drugs, impact on efficacy and safety, risks of clinically significant interaction effects. Valuation techniques using reference sources - Swedish Physicians Desk Reference, Beers Criteria, The American Geriatric Association.

33.5% of patients receiving drug potentially recommended list Beers, of which 24.5% with a high security risk.

632 patients treated with 414 drug combinations, drug interactions safety profile analysis demonstrates their irrationality. Most often – 29.2% of the drug combination found cephalosporins+NSAIDs. In 107 cases, we used a combination of ceftriaxone+ furosemide, which enhances the nephrotoxic effects of cephalosporins. The 1.8% (3) simultaneously combined drugs of the group of cephalosporins, aminoglycosides plus furosemide, each of which has nephrotoxicity and ototoxic action. 3% of the drug combinations include the fluoroquinolones + NSAIDs, trombokard + levofloxacin that increase the risk of central nervous system excitation and convulsions.

Total of 72 combinations of drugs have been reported which comprises a drug-type "C". Potentially clinically significant drug interactions have been - 22 furosemide + enalapril, 34 digoxin+furosemide, 16 digoxin + spironolactone.

Inclusion of drugs "type C" the combination increases the risk of potentially clinically significant adverse drug reactions, for the prevention of which may require dose adjustment.

The pharmacotherapy of elderly is characterized by the high level (76,1%) of an irrational combination of drugs, frequent appointment (33,5%) of the drugs which aren't recommended elderly, not compliance of clinical need in case of VP (18%) that leads to decrease in efficiency and safety of therapy.

PHARMACOKINETICS AND SAFETY PROFILE OF BLESELUMAB (ASKP1240) IN PATIENTS WITH MODERATE-TO-SEVERE PLAQUE PSORIASIS: RESULTS FROM A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SEQUENTIAL, MULTIPLE-DOSE ESCALATION STUDY

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Background: This study evaluated pharmacokinetic (PK) parameters, safety, and tolerability of bleselumab – a fully-humanized anti-CD40 monoclonal recombinant IgG4.
Methods: Patients with moderate-to-severe psoriasis were randomized on day 1 to receive one of five treatments on days 1, 15 and 29: intravenous bleselumab 0.1mg/kg, 0.3mg/kg, 1.0mg/kg, or 3.0mg/kg, or placebo. Safety-analysis set (SAS): all patients who received bleselumab or placebo; PK-analysis set (PKAS): patients in the SAS with ≥1 quantifiable serum concentration of bleselumab. Serial blood samples were collected after each dose, and bleselumab serum concentration was measured. Area under the concentration–time curve (AUC_{336h}) and maximum serum concentration (C_{max}) after each dose were determined using non-compartmental methodology. Dose proportionality of AUC_{336h} and C_{max} after each dose was analyzed using separate power models. Adverse events and changes in laboratory parameters from baseline were assessed.
Results: Sixty patients were randomized and included in the SAS (bleselumab, n=49; placebo, n=11); 47 formed the PKAS. C_{max} and AUC_{336h} were more than dose proportional at ranges 0.1mg/kg to 3.0mg/kg and 0.3mg/kg to 3.0mg/kg, suggesting that bleselumab showed nonlinear pharmacokinetics (**table**). There were no clinically-significant infusion reactions, cytokine-release syndrome, or thromboembolic events. Four patients (8.5%) had alanine aminotransferase levels that were >3xULN at some point during the study (two patients each in the 1.0mg/kg and 3.0mg/kg groups).

Table.

	Bleselumab Dose (mg/kg)	Day 1	Day 15	Day 29
Mean (± SD) C_{max}, µg/mL	0.1	0.264 ± 0.140	0.522 ± 0.371	0.402 ± 0.291
	0.3	4.24 ± 1.66	4.26 ± 1.58	4.36 ± 1.62
	1.0	27.0 ± 6.00	28.7 ± 5.56	32.9 ± 7.04
	3.0	77.3 ± 17.4	90.7 ± 20.8	101 ± 28.8
Mean (± SD) AUC_{336h}, µg·h/mL	0.1	0.727 ± 1.22	10.1 ± 28.1	2.27 ± 3.35
	0.3	174 ± 77.5	333 ± 135	161 ± 66.6
	1.0	1865 ± 672	2373 ± 998	3046 ± 1098
	3.0	9398 ± 1990	12,311 ± 3612	14,543 ± 4495

Conclusions: Bleselumab was generally well tolerated, showing nonlinear pharmacokinetics after single and multiple doses. Increases in bleselumab C_{max} and AUC_{336h} were greater than dose proportional after single- and repeated-doses of 0.1mg/kg to 3.0mg/kg iv.**ClinicalTrials.gov:** NCT01585233

PATTERNS OF USE AND DIVERSION OF BENZODIAZEPINES AND RELATED SUBSTANCES IN FRANCE: RESULTS OF THE OSIAP SURVEY

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