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PHARMACEUTICALS

XEL1005/01 EudraCT Summary Statement

Study title: 'Plasma levels of crystalline degradation product 1 (CDP-1) in vancomycin- treated patients with normal or impaired renal function''
Protocol code / Study Number: CSP.XEL1005,
EudraCT No. 2015-005349-29

Zagreb, 10/Sep/2021

To whom it may concern,

In order to comply with Commission Guideline (*Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006*) and as requested *in the Joint Letter by the European Comission, EMA and HMA, June 2019*, a synopsis of the prematurely terminated XEL1005/01 study and available results are provided below.
The study was prematurely terminated by the Sponsor after 14 months due to inability to complete the recruitment into one out of two study cohorts (Cohort B) within a reasonable period.

With kind regards,

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Study synopsis

Study title	Plasma levels of crystalline degradation product 1 (CDP-1) in vancomycin treated patients with normal or impaired renal function.
Study code / EudraCT Number	XEL1005/01 / 2015-005349-29
Coordinating Investigator	Professor Bruno Barišić, MD, PhD
Study sites	• University Hospital for Infectious Diseases „Dr. Fran Mihaljević", Department for Intensive Care Medicine and Neuro-infectology, Zagreb, Croatia. •Sestre milosrdnice University Hospital Center, Department for Hematology, Zagreb, Croatia.
Publication	None.
Study period	• Date of the first patient first visit (FPFV): 20-APR-2016 • Date of the last patient last visit (LPLV): 31-MAY-2017
Phase of development	Phase IV
Objectives	• To collect information on CDP-1 levels in plasma after repeated IV dosing of vancomycin in patients with normal and impaired kidney function, respectively. • To explore if there is a difference in systemic exposure to CDP-1, relative to vancomycin, between patients with normal and impaired kidney function.

Methodology	Blood samples for the measurement of CDP-1 and vancomycin concentration in plasma were collected from patients otherwise treated with intravenous (IV) vancomycin at presumed steady state. The samples were collected from patients with normal renal function, after at least three days of treatment with 1 g vancomycin q12h (Cohort A), and from patients with impaired kidney function, after at least five days of q24h vancomycin treatment with corresponding daily dose adjusted to renal function (Cohort B). On the blood sampling day (study Day 1), the same dose of vancomycin as previously administered was infused over 120 min. and blood samples (2 mL each) were collected pre-dose and at 1, 2 (end of infusion), 2.5, 3, 4, 5, 8 and 12 h after the start of infusion, and in Cohort B only, at 24 h as well. At the end of infusion, the infusion solution retained in the dead space of infusion system was also collected for determination of CDP-1 and vancomycin concentration. Patient's participation in the study ended after collection of the last blood sample. CDP-1 and vancomycin concentrations in plasma were subsequently analyzed using a validated liquid chromatography tandem mass spectrometry method, with protein precipitation sample preparation. The lower limit of quantification was 0.02 and 0.1 µg/mL, respectively. Pharmacokinetic (PK) parameters for both compounds, including the area under the concentration time curve during a dosing interval (AUCW), maximum observed concentration in plasma (Cmax), time to Cmax (Tmax), the concentration at the end of the dosing interval (Ctrough), total clearance from plasma (CLss), and volume of distribution (Vss) were calculated using standard noncompartmental analysis. CDP-1 and vancomycin concentrations in infusion solution were analyzed using a validated ultrahigh performance liquid chromatography method
Number of patients	Planned: 16 (eight per Cohort). Included: 13 (10 in Cohort A and three in Cohort B). Completed: 13 (10 in Cohort A and three in Cohort B). Analyzed: 10 (seven in Cohort A and three in cohort B)
Diagnosis	Any infectious disease or condition that requires vancomycin therapy.
Main criteria for inclusion and exclusion	Inclusion criteria (Cohort A) 1. Male or female 18 years of age or older. 2. Creatinine clearance (CLCR) ≥ 90 mL/min (estimated from serum creatinine using the Cockroft-Gault formula). 3. At least three days of IV treatment with vancomycin at a dose of 1 g every 12 hours. 4. Capable to understand and provide informed consent as evidenced by signed informed consent. Inclusion criteria (Cohort B) 1. Male or female 18 years of age or older.

	2. CLCR < 50 mL/min (estimated from serum creatinine using the Cockcroft Gault formula). 3. No indication for continuous hemofiltration based on the Investigator's opinion. 4. At least five days of IV treatment with vancomycin at a dose which in the investigator's opinion corresponds to a dose of 2 g/day in patients with normal renal function, given once daily after the loading dose selected by the investigator. 5. Capable to understand and provide informed consent as evidenced by signed informed consent. Exclusion criteria (both cohorts) 1. Human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection, as evidenced by medical history or positive result of serological testing. 2. Pregnancy, if evident from medical history. 3. Class II or III obesity (body mass index ≥35). 4. Treatment with medications which interfere with serum creatinine assay (e.g., barbiturates, cefazolin, ceforanide, cefoxitin, cefpirome, levodopa, methyldopa), or decrease CLCR without effect on glomerular filtration rate (cimetidine, pyrimethamine, trimethoprim), within one week prior to screening or during the screening period. 5. Presence of risk factors which in the investigator's opinion may preclude completion of blood sampling according to the protocol.
Test product, dose and mode of administration	The patients were to receive any of the vancomycin products approved in Croatia, routinely used at the clinical site. Vancomycin solution for infusion was prepared in line with manufacturer's instructions and standard practice, and was infused IV over 120 min.
Duration of treatment	Not applicable; the samples were collected from patients otherwise treated with vancomycin, at anticipated steady state and over 12-24 h.
Reference therapy	Not applicable.
Criteria for evaluation (endpoints)	• CDP-1 load after IV dosing of vancomycin and CDP-1-to-vancomycin ratio in infusion solution. • PK parameters for vancomycin in patients with normal or impaired renal function, respectively, including AUCW, Cmax, Tmax, Ctrough and CLss. • PK parameters for CDP-1 in patients with normal or impaired renal function, respectively, including AUCW, Cmax, Tmax, Ctrough and CLss. • Dose-normalized CDP-1 AUCW in plasma in patients with normal or impaired renal function, respectively. • CDP-1 AUCW relative to vancomycin AUCW in plasma in patients with normal or impaired renal function, respectively.

Statistical methods	Hypotheses: This was an exploratory study with no formal hypothesis testing. Analysis populations: All eligible patients who completed the study without a major protocol deviation were included in analysis. Since blood sampling during the infusion (1 h time point) was subsequently added to the protocol, PK data were analyzed in two populations of patients: • Per Protocol (PP) population, defined as all patients who completed the study without a major protocol deviation and had PK data calculated by ignoring the 1 h time point, if available, and • Enriched Plasma Profile (EPP) population, defined as all patients who completed the study without a major protocol deviation and had PK data calculated using all plasma concentration data available. The EPP population was to be considered primary if in the subset of patients with 1 h plasma concentration data, a difference in the AUCW calculated with and without the 1 h time point was <5% for both vancomycin and CDP-1. Otherwise, the PP population would be considered primary. Methods of analysis: Demographic and other baseline data, including CLCR, as well as vancomycin dosing details and body temperature on the blood sampling day, were listed by patient and summarized by cohort using descriptive statistics. Actual vancomycin dose and CDP-1 load were calculated from observed concentrations in infusion solution and volume of infusion solution. The CDP-1/vancomycin ratios in infusion solution were derived and summarized by cohort. Observed plasma concentrations of vancomycin and CDP-1 were summarized by cohort and time point. Individual plasma concentration-overtime profiles and mean profiles by cohort were plotted. PK parameters for CDP-1 and vancomycin were calculated using standard non-compartmental analysis. In patients with 1 h plasma concentration data, AUCW and other PK parameters of both compounds were calculated with and without 1 h values. The peak, trough and total exposures for both analytes were normalized according to actual vancomycin dose. Individual dose-normalized CDP-1/ vancomycin AUCW ratios were calculated. All PK data were listed by patient and summarized by cohort. The relationship between CLCR and the CDP-1/ vancomycin AUCW ratio was graphically explored. Sample size calculation: In view of exploratory nature of the study, the sample size of eight evaluable patients per cohort was arbitrarily determined.
Summary - Conclusions The study was prematurely terminated by the Sponsor after 14 months due to inability to complete the recruitment into Cohort B within a reasonable period of time.	

Patient disposition: Thirteen patients in total were included in the study, 10 in Cohort A and three in Cohort B, and none was prematurely withdrawn. Seven patients from Cohort A and three from Cohort B completed the study without a major protocol deviation and were included in the PP/EPP population.
Study population: Key characteristics of the PP/EPP population are summarized below.

Characteristic	Descriptor	Cohort A (N=7)	Cohort B (N=3)	Overall (N=10)
Age (years)	Mean (SD)	59.0 (4.9)	62.0 (6.0)	59.9 (5.1)
Sex (male/female)	n (%) / n (%)	5 (71.4) / 2 (28.6)	1 (33.3) / 2 (66.7)	6 (60) / 4 (40)
Race (white)	n (%)	7 (100)	3 (100)	10 (100)
Body Mass Index (kg/m2)	Mean (SD)	29.7 (3.9)	29.4 (5.2)	29.6 (4.0)
CLCr (mL/min)	Mean (SD)	103.0 (6.5)	35.0 (13.5)	82.6 (33.9)
Vancomycin treatment duration period to Day 1 (days)	Median (range)	7 (3-13)	6 (5-20)	7 (3-20)

All patients had some comorbidities and have received medications other than vancomycin. Three vancomycin products were used in total and were equally distributed across the cohorts. Vancomycin dosing regimen in all Cohort A patients was 1 g q12h; in Cohort B, two patients were receiving 1 g q24h, and the remaining one 1.5 g q24h. On the blood sampling day, the same dose as previously used was administered, diluted in normal saline. The volume of infusion solution was 110-270 mL in Cohort A and 260-265 mL in Cohort B. In both cohorts the infusion time ranged 118-120 min.
Pharmacokinetic results: In all patients both vancomycin and CDP-1 were quantifiable in plasma at all time points, including pre-dose samples. Pre-dose concentrations of both analytes, designated as Ctrough, corresponded to concentrations observed at the end of the dosing interval (Clast), indicating the steady state.
In the subpopulation of patients with the 1 h time point, the estimated geometric mean AUCtau (-1 h)/ AUCtau (+1 h) ratio was 0.97 for vancomycin and 0.994 for CDP-1, so the EPP population was considered the primary population for interpretation of all data.
Steady state PK parameters for the EPP population are shown on the next page. Actual doses for vancomycin and CDP-1 were used to calculate CLss for vancomycin and CDP-1, respectively. The CLss calculated for CDP-1 is likely underestimated in this case, because the measured CDP-1 exposure is the result of both administered CDP-1 and CDP-1 formed by vancomycin degradation in bloodstream. An accurate estimation of CDP-1 CLss would require CDP-1 administration only. The half-life for vancomycin and CDP-1 could not be estimated because the extrapolated AUC was greater than 20% of the total AUC from time zero to infinity.

Summary of steady state PK parameters (EPP population)

PK parameter	Geometric mean [90% confidence interval]			
	Cohort A (N=7)		Cohort B (N=3)	
	Vancomycin	CDP-1	Vancomycin	CDP-1
AUCτ (h·µmol/L)	169 [128, 223]	2.95 [2.00, 4.35]	777 [293, 2060]	24.1a [0.174, 3330]
Cmax (µmol/L)	26.0 [20.4, 33.1]	0.407 [0.293, 0.566]	56.6 [22.4, 143]	1.36 [0.339, 5.47]
Tmax (h)#	2.00 [2.0-2.50]	2.00 [2.00-3.00]	2.00 [1.0-2.27]	2.00 [1.00-2.27]
Ctrough (µmol/L)*	8.40 [6.33, 11.1]	0.166 [0.111, 0.246]	24.9 [8.10, 76.2]	1.01 [0.247, 4.13]
Clast (µmol/L)**	9.56 [7.18, 12.7]	0.183 [0.119, 0.281]	24.7 [9.00, 67.8]	1.10 [0.250, 4.82]
CLss (mL/min)	55.7 [45.2, 68.8]	4.04 [1.57, 10.4]	14.8 [6.03, 36.1]	1.14a [0.00687, 188]
Vss (L)	51.1	4.89	41.6	6.10a

	[35.8, 73.0]	[2.12, 11.2]	[17.0, 102]	[0.00945, 3940]
DNAUCτ ((h·µmol/L)/µmol)§	0.299 [0.171., 0.522]	1.13 [0.240, 5.32]	0.00521 [0.00203, 0.0134]	0.032a [0.000118, 8.66]
DNCmax ((µmol/L)/ µmol)§	0.0459 [0.0286, 0.0737]	0.0822 [0.0195, 0.348]	0.000721 [0.00033, 0.00157]	0.00198 [0.000224, 0.0175]
DNClast ((µmol/L)/ µmol)§	0.0169 [0.00891, 0.0321]	0.0359 [0.00619, 0.208]	0.000323 [0.000109, 0.000961]	0.0016 [0.000142, 0.0179]

NOTES: *Concentration in the pre-dose sample; **Concentration at the end of the dosing interval; #Tmax is expressed as median [range]; §Normalized to actual vancomycin dose; aN=2 because the elimination rate constant for CDP-1 and related PK parameters could not be estimated for one patient

Summary of CDP-1 / vancomycin ratios in infusion solution and plasma

	Geometric mean [90% confidence interval]	
	Cohort A (N=7)	**Cohort B (N=3)**
CDP-1 / vancomycin ratio in infusion solution	0.00126 [0.000464 to 0.00344]	0.00144 [0.0000964 to 0.0216]
CDP-1 DNAUCτ/ vancomycin DNAUCτ ratio in plasma	0.0174 [0.0134 to 0.0226]	0.0350a [0.00764 to 0.160]

NOTES: aN=2 because the elimination rate constant for CDP-1 could not be estimated for one patient

CDP-1 load was generally low (median 0.485 mg, i.e., 0.335 µmol) but highly variable; range 0.426-11.7 mg (CV 133%). The geometric mean CDP-1/vancomycin DNAUCτ ratio was approximately 14-24 fold higher in comparison to the CDP-1/vancomycin ratio in infusion solution, suggesting that CDP-1 is formed as a metabolite in vivo. The CDP-1/vancomycin DNAUCτ ratio was approximately 2-fold higher in Cohort B (n=2) compared to Cohort A, however, in one of the two Cohort B patients with respective data, this ratio was in the range of ratios observed in Cohort A.

Conclusion: CDP-1 was quantifiable in plasma after repeated vancomycin IV dosing across the dosing interval. Peak levels occurred at the end of vancomycin infusion and coincided with vancomycin peaks. Higher maximum levels and exposure were observed for both vancomycin and CDP-1 in Cohort B compared to Cohort A, because Cohort B patients have received higher vancomycin doses, relative to actual CLCR values. CDP-1 exposure was more variable than vancomycin exposure, but was generally low and did not exceed 5% of vancomycin exposure. For both compounds, the CLss was lower in patients with renal impairment, with no difference in the Vss. CDP-1 CLss could not be reliably estimated due to unknown rate of CDP-1 formation in vivo; Vss was around 5-6 L. The CDP-1/vancomycin ratio was 14-24 fold higher in plasma than in infusion solution, implying that CDP-1 is formed as a metabolite in vivo. While the ratio was higher in patients with renal impairment, this result was inconclusive as it was based on data from two Cohort B patients only.