Title:

A single-centre, open, controlled, randomised cross-over study in healthy male and female volunteers to evaluate the pharmacokinetics of cholyl-lysyl-fluorescein (NRL972) in the presence of medication-induced changes in cytochrome P450 or biliary transporter proteins.

Part X: Extension study

Norgine Study №: NRL972-12/2008 (IN-X)

Investigators:

PD Dr. med. Emil Gatchev (Investigator), Dr. V. Pajantova and Dr. E. Kolev (Co-/Sub-Investigators)

Study centre(s):

Dept. Clinical Pharmacology & Therapeutics, MHAPT "Zaritza Johanna", Sofia – Bulgaria

Publication (reference):

n.a.

Study period:	**Clinical Phase:** I
19 Feb 2009 (first screening) until 07 Apr 2009 (last end-of-trial visit)	

GCP-compliance:

The study was planned, conducted, analysed and reported in accordance with the pertinent GCP-Guidelines.

Objectives of the study:

To provide an extension and endorsement of the findings of the previous interaction studies NRL972-02/2007 (IN-C) and NRL972-04/2007 (IN-E) and to resolve issues with the observed time courses of the plasma concentrations presumed to have been related to erroneous PK-sampling via the application/injection catheter

Study design:

Half of the subjects were enrolled into the extension of study IN-C (Part XC of the present study); the other half into the extension of study IN-E (Part XE). The study was conducted in a single-centre, controlled, open, within-subject three-way cross-over fashion to describe and compare the single-dose pharmacokinetics of NRL972 after pre- and co-administration of two possibly interacting agents (T1 [Extension to IN-C: Erythromycin; Extension to IN-E: Phenobarbital] & T2 [Extension to IN-C: Tacrolimus; Extension to IN-E: Ethanol]) with the pharmacokinetics without concomitant medication (R).

The treatments were randomly assigned in period-balanced sequences; profiling days D01 of each period were at least 2 weeks apart for wash-out purposes.

Number of subjects:

Twelve healthy volunteer subjects (six males, six females)

Diagnosis and criteria for inclusion:

Male and female (of non-childbearing potential or while taking medically appropriate contraception), Caucasian subjects, 21 – 40 years of age, Body Mass Index (BMI) of 20 to 26 $kg.m^{-2}$ and body weight (BW) of 50 to 100 kg who were confirmed to be healthy on the basis of an extensive screening investigation (medical history, physical examination, vital functions, 12-lead ECG, clinical laboratory safety tests [haematology, clinical chemistry, urinalysis, serology, screening tests for substances of abuse and alcohol]), and who were able and willing to provide informed consent.

Test product, dose, batch N°:

Cholyl-L-lysine-fluorescein (SYN: CLF, Code: NRL972), Norgine Ltd., solution for iv injection (2 mg NRL972 in 5 mL solution for injection), 2 mg (5 mL) administered once by 15-second iv injection on three occasions
IMP Batch-N°: NOR-p004

Reference product, batch N°:

Not applicable

Duration of treatments:

One single administration of 2 mg NRL972 on the morning of D01 on three periods at least 2 weeks apart

Schedule:

- Screening (SCR) visit: Eligibility assessment (EA): between 14 and 2 days before admission for the first period
- Three study periods; for each period: hospitalisation from the evening of D-1 until 12:00 hours after dosing
- Wash-out interval: at least 2 weeks between consecutive profiling days D01
- End-of-trial (EOT): within one week after administration of NRL972 in the last period

CLINICAL PHARMACOLOGY FINDINGS

Subject disposition:

- Eighteen (18) subjects were screened for enrolment, six subjects were not included in the study (reasons listed in Section 10.1). All subjects participating in Part XE had previously participated in study IN-E. Four subjects enrolled in Part XC had previously participated in study IN-C, two further subjects in Part XC had previously participated as control subjects in the study NRL972-08/2007 (REN [ACPS615]).
- Twelve (12) subjects were enrolled. One subject (X011) was discontinued prematurely from part XE of the study after having completed periods PE1 and PE2 (treatments R and T2), due to an adverse event at the start of the preparatory pre-treatment with Phenobarbital (treatment T1). The subject was not replaced. All of the other 11 subjects completed the study for all three scheduled periods.
- All 12 subjects were included in the safety dataset; descriptive pharmacokinetic analyses were carried out for all data as available (ITT) and for the subset of subjects who completed the study for all three scheduled periods (PP).

Demographics

All 12 subjects (six males, six females) were Caucasians: mean (± SD) age: 30.3 ± 5.4 years [range: 22 to 39]; mean body weight: 71.3 ± 12.2 kg [range: 52 to 94]; mean BMI: 23.9 ± 1.8 kg.m^{-2} [range: 20.7 to 26.0].

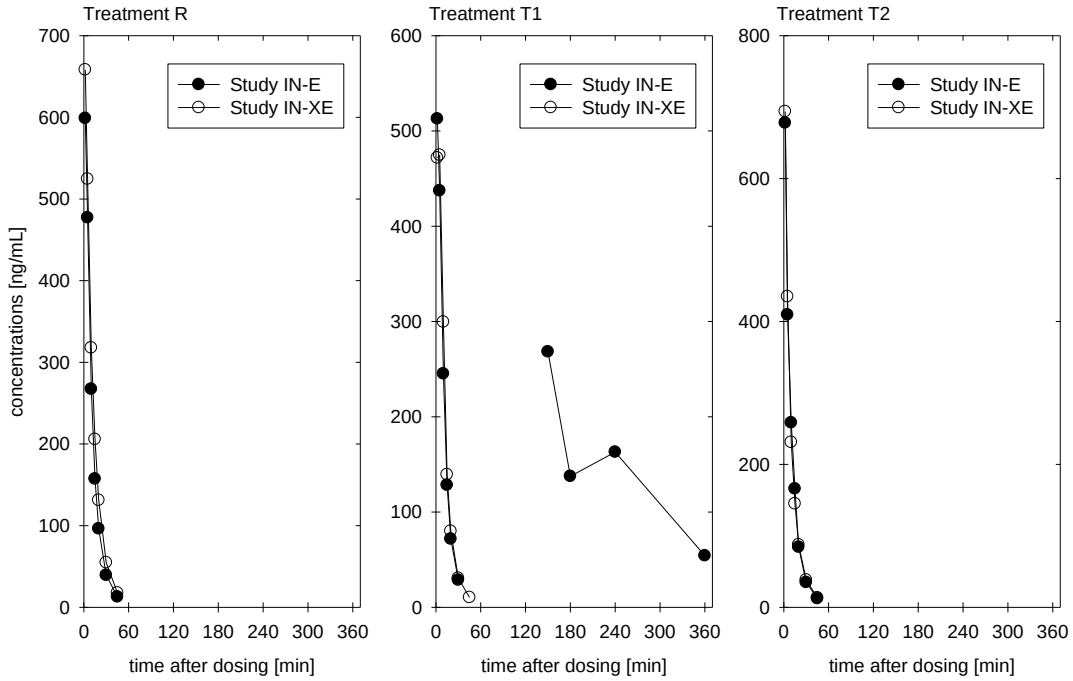
All subjects were judged to be healthy upon in-depth evaluation at the screening visit.

Pharmacokinetics of NRL972

The pharmacokinetic extension data on the drug-drug interaction between NRL972 and
1) Erythromycin and Tacrolimus, and
2) Phenobarbital and Ethanol
are reported in the reports for the respective studies (IN-C and IN-E).

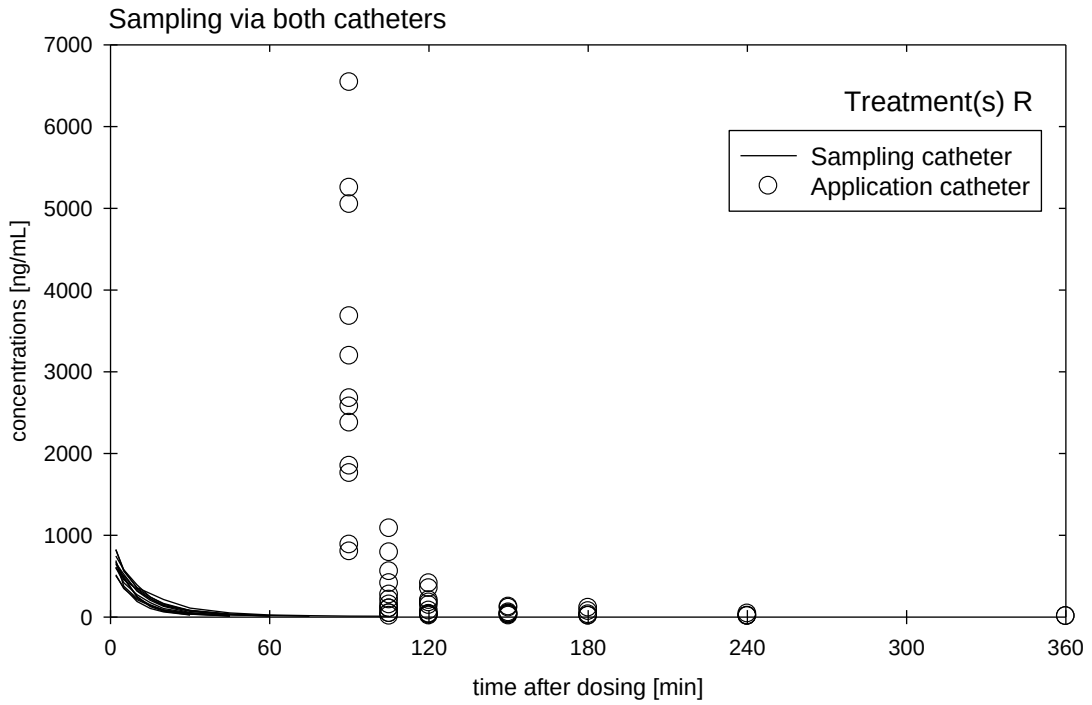
The present report only relates to the observations related to the PK-sampling via the injection catheter.

The individual time courses of the plasma concentrations of NRL972 of the present study (sampling via sampling catheter) were in excellent agreement with those during their previous participation (studies IN-C, IN-E, or REN) over the first hour after injection of NRL972. The distortions of the profiles seen previously, by unexpectedly quantifiable concentrations later in the time course, were not observed in the present study when special precautions were taken not to sample via the application catheter; this is shown below for subject X012 (Part XE):



Subject E001 / X012

No NRL972 had been quantifiable in plasma from blood drawn via the application catheter prior to injection of NRL972. The application catheter was not flushed after NRL972 injection and no blood samples were taken via this catheter before sampling at 1:30 hours after injection. None of the plasma samples taken via the sampling catheter had quantifiable concentrations beyond 1:45 hours and only 1/12 subjects had quantifiable concentrations at 1:30 and 1:45 hours after injection. In contrast, very high concentrations of NRL972 were detectable in plasma from blood drawn via the application catheter at 1:30 hours after dosing; this is shown in the following graph for the pooled control treatments (treatment R; N:12):



The descriptive statistics of the plasma concentrations of NRL972 (ng/mL) from blood sampled (first and second sample, 01:30 and 01:45 after dosing) via the application catheter were as follows (MX: arithmetic mean; SD: arithmetic standard deviation; gM: geometric mean; gCV: geometric coefficient of variation; MIN: minimum observed value; MED: median; MAX: maximum observed value):

Part:	**ALL**	**ALL**	**XC**	**XC**	**XC**	**XC**	**XE**	**XE**	**XE**	**XE**
TR:	**R**	**R**	**T1**	**T1**	**T2**	**T2**	**T1**	**T1**	**T2**	**T2**
Time:	**01:30**	**01:45**	**01:30**	**01:45**	**01:30**	**01:45**	**01:30**	**01:45**	**01:30**	**01:45**
MES	**ng/ml**	**ng/ml**	ng/ml	ng/ml	ng/ml	ng/ml	**ng/ml**	**ng/ml**	**ng/ml**	**ng/ml**
N	12	12	6	6	6	6	5	5	6	5
MX	3054	317	3145	251	2704	349	1805	115	2001	240
SD	1787	337	2359	248	1678	264	1126	83	1761	225
gM	2555	170	2569	156	2069	234	1575	81	1437	149
gCV	0.74	2.07	0.77	1.60	1.13	1.56	0.62	1.42	1.18	1.74
MIN	802	14.6	1059	31.5	528	57	764	17.3	343	32
MED	2627	182	2326	132	3145	393	1558	132	1536	136
MAX	6542	1084	7565	639	4415	615	3716	222	5270	541

SAFETY

Injection of NRL972 on three occasions and the potentially interacting medications Erythromycin and Tacrolimus were clinically very well tolerated. Pretreatment with Phenobarbital and Ethanol showed clinical effects in accordance with their known properties. In Part XC there were two AEs in 2/6 subjects. In Part XE, there were 11 AEs in 5/6 subjects. Most of the AEs were mild and of little clinical relevance. In one subject there was a nephrocolic-episode due to nephrolithiasis with onset in the late afternoon and which progressed through the night of the first preparatory treatment day with Phenobarbital (D-8). The subject was discontinued from the trial. There were no serious AEs.

Further safety information is listed individually and will be analysed and discussed extensively in the context of the further safety information that will be reported for the same treatments in the study reports of the original interaction studies IN-C and IN-E.

CONCLUSION

- Very high NRL972 concentrations well beyond what could be expected for the systemic pharmacokinetics of NRL972 were found in plasma upon first post-dose sampling via the application catheter at 1:30 hour after dosing (for the pooled treatments R: 3054 ± 1787 ng/mL; range: 802 to 6542 ng/mL); when sampling a second time, 15 minutes later, the average concentrations were about ten times less (for the pooled treatments R: 317 ± 337 ng/mL; range: 15 to 1084 ng/mL), but in the region of what might be expected for the systemic pharmacokinetics of NRL972 over the first 10-15 minutes after NRL972 injection.
- Erroneous sampling of blood for pharmacokinetic determinations via the application catheter even in the late course of the investigations may lead to artificial distortions of the time courses of plasma concentrations with unexpectedly high plasma concentrations due to sample contamination by residual NRL972 in the application catheter.
- This phenomenon provides adequate explanation for the observed distortions of some of the pharmacokinetic profiles in previous studies NRL972-02/2007 (IN-C), NRL972-04/2007 (IN-E) and NRL972-08/2007 (REN). These distortions can be accepted to be outlying values due to procedural error; accordingly they can be discarded from the pharmacokinetic evaluations of the primary objectives of these studies.

11 Jan 2010

Norgine discontinued the development of NRL972 in July 2013.