Title:

A single-centre, open, uncontrolled study in healthy male and female volunteers to describe the plasma pharmacokinetics of cholyl-lysyl-fluorescein (NRL972) during and after a constant rate i.v. infusion

NORGINE Study №: NRL972-03/2005 (IV)

Investigators:

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Study centre(s):

Balatonfüred, Hungary

Publication (reference):

n.a.

Study period:	**Clinical Phase:** I
Part A: 6 Jun 2006 (screening of first subject) – 26 Jun 2006 (end-of-trial in last subject) Part B: 15 Nov 2006 (screening of first subject) – 13 Feb 2007 (end-of-trial in last subject)	

GCP-compliance:

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

Objectives of the study:

To describe the plasma pharmacokinetics of NRL972 during and after a 2-hour iv infusion of 5 mg/hour NRL972 (Part A) and 15 mg/hour NRL972 (Part B); additionally, the study provides information on the safety and tolerability of intravenous NRL972 under these conditions.

Study design:

Single-centre, open, uncontrolled, single-dose trial in young healthy men and women investigating the pharmacokinetics of a single 2-hour iv infusion of 5 mg/hour NRL972 (Part A) and 15 mg/hour NRL972 (Part B). Each subject was studied on one occasion; a single dose of NRL972 was administered once (time 0:00 = start of the infusion which lasted for 2 hours) after an overnight fast and rest.

Number of subjects:

In each part of the two parts of the study, twelve healthy volunteer subjects (six males, six females) were investigated.

Diagnosis and criteria for inclusion:

Male and female (of non-childbearing potential or while taking medically appropriate contraception), Caucasian subjects, 25 – 40 years of age, Body Mass Index (BMI) of 22 to 26 $kg.m^{-2}$ and body weight (BW) of 50 to 100 kg who were confirmed to be healthy on the basis of 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 (synonyms: CLF, cholyl-lysyl-fluorescein; INN Fluorescein lisicol tri-sodium salt; Development Code: NRL972), NORGINE Ltd., solution for iv injection (using 2 mg NRL972 in 5 mL solution for injection), 10 mg (Part A) and 30 mg (Part B) were administered by 2-hour iv infusion on one occasion in each subject. IMP Batch-N°: NOR-p004

Reference product, batch N°:

Not applicable

Duration of treatments:

One single administration of 10 mg (Part A) or 30 mg (Part B) NRL972 by 2-hour iv infusion on the morning of Day D01 on one occasion

Schedule:

- EA/SCR: screening visit within 14 and 2 days before hospitalisation: assessment of eligibility
- One study phase (period) per subject:
  - Each subject was hospitalised from the evening of Day D-1 until 12:00 h after the start of the infusion (evening of D01)
- EOT: end-of-trial evaluation within 1 week after study day D01

CLINICAL PHARMACOLOGY FINDINGS

Subject disposition:

- Fifty subjects (Part A; 26; Part B: 24) were screened for enrolment. Twenty-three subjects (Part A: 14; Part B: 9) were not enrolled (reasons listed in Section 10.1).
- Twenty-seven (27) subjects were enrolled Part A: 12; Part B: 15). All enrolled subjects were assigned to active treatment and treated once. No subject was discontinued prematurely from the study
- In Part A, 12 subjects were enrolled; all 12 subjects completed the study in accordance with the protocol; all twelve were included in the dataset for safety and PK analysis.
- In Part B, 15 subjects were enrolled; due to concerns about the implications of short interruptions of the iv infusion, the data from three subjects (R108, R111, and R112) were excluded from the per-protocol PK dataset (PP); these subjects were replaced by subjects R120, R121, and R122; all fifteen subjects are part of the dataset for safety analysis and the ITT dataset for PK-analysis; subjects R108, R111, and R112 were excluded from the PP dataset for PK-analysis.
- No subject was discontinued prematurely from the study.

Demographics

Part-A: All 12 subjects (six males, six females) were Caucasian: mean (± SD) age: 28.5 ± 2.3 years [range: 25 to 31]; mean body weight: 69.6 ± 12.3 kg [range: 53 to 90]; mean BMI: 23.55 ± 1.42 kg.m-2 [range: 22.13 to 25.85].

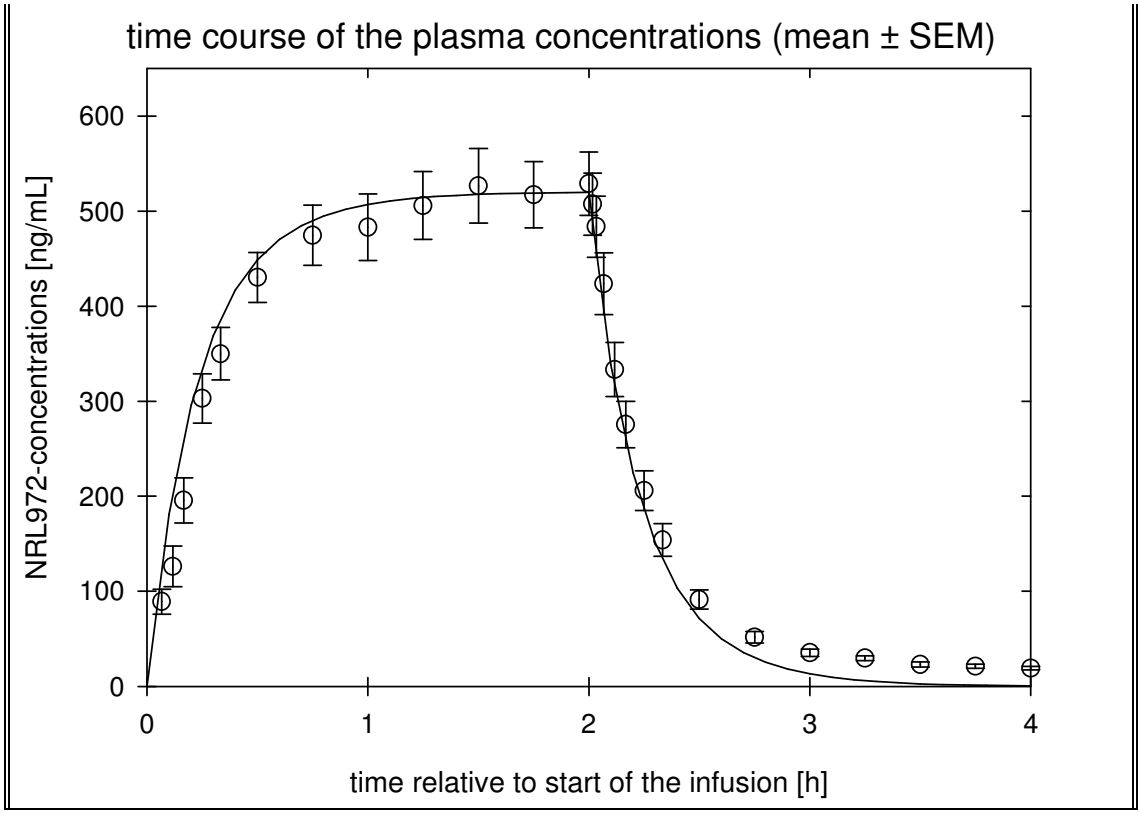
Part-B: All 15 subjects (six males, nine females) were Caucasian: mean (± SD) age: 31.4 ± 3.4 years [range: 27 to 37]; mean body weight: 71.6 ± 11.1 kg [range: 56 to 93]; mean BMI: 24.31 ± 1.42 kg.m-2 [range: 22.04 to 25.85].

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

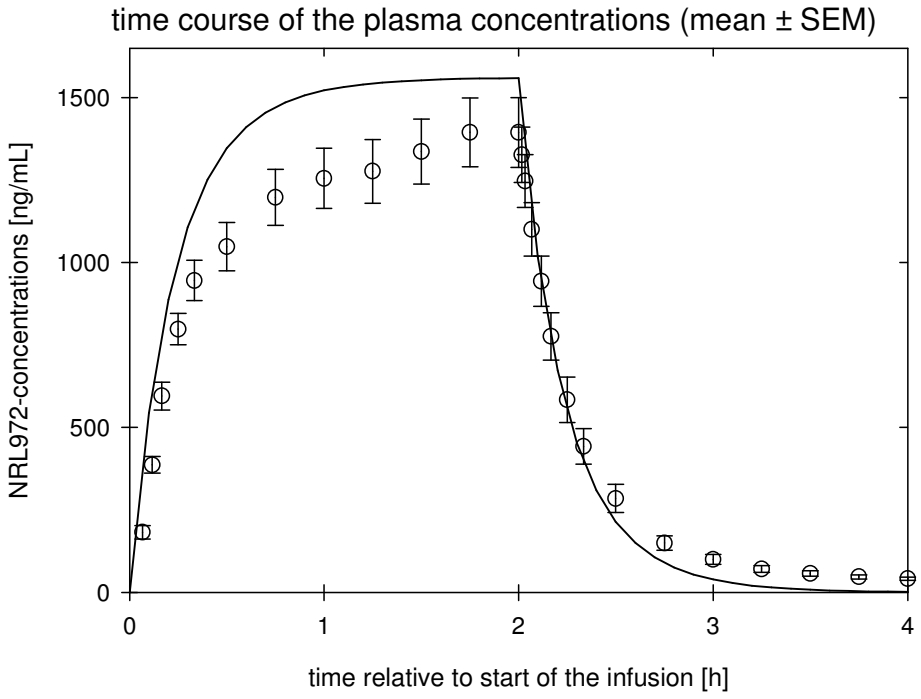
Pharmacokinetics – Time courses of the plasma concentrations

The time courses of the observed median plasma concentrations during and after the infusion of 5 mg and 15 mg NRL972 per hour for 2 hours were as follows (relative to the predicted levels based on simulations using the data form Norgine trial NRL972-02/2003 (ACPS)):

Part A: 2-hour infusion of 5 mg/hour NRL972


time course of the plasma concentrations (mean ± SEM)
NRL972-concentrations [ng/mL]
600
500
400
300
200
100
0
0
1
2
3
4
time relative to start of the infusion [h]

Part B: 2-hour infusion of 15 mg/hour NRL972



Pharmacokinetics – PK methods & variables

Ceq: variables based on the assumed equilibrium at the end of the infusion: equilibrium concentration (CEQ); total clearance (CL); CL by kg body weight (CL/BW)

2P-ANA: fractional concentration recovery in the post-infusion course: C(30):C(10)- and C(30):C(15)-ratio

I-NCA: non-compartmental analysis (NCA) of the full course of the concentrations during and after the infusion: maximum observed plasma concentration (C_{max}); time of C_{max} (t_{max}); CL, CL/BW; apparent terminal disposition half-life (t½)

PI-Full: NCA of the post-infusion course including all values as quantifiable: t_{max}; C_{max}; t½

PI-Short: NCA of the post-infusion course up to one hour after the end of infusion: t_{max}; C_{max}; t½ ;

FIT-2C: fitting the full course during and after infusion to an open 2-compartmental model: estimated volume of the central compartment (V_1); estimated volume of the peripheral compartment (V_2); rate constant for the transfer from V_1 to V_2 (k_{12}); rate constant for the transfer from V_2 to V_1 (k_{21}); elimination rate constant outside of V_1 (k_{10}); estimated total volume of distribution (Vdss=V_1 + V_2); half-lives of the 1st (fast) and 2nd (slower) exponential disposition phase (t½ (1), and t½ (2)); CL and CL/BW

The descriptive statistics of the main variables (N: number of quantifiable data, MX: arithmetic mean, aCV: arithmetic coefficient of variation, gM: geometric mean; gCV: geometric coefficient of variation; MIN: minimum value; MED: median; MAX: maximum observed value) were:

Part A: 2-hour infusion of 5 mg/hour NRL972 (PP=ITT; N:12)

METH	Variable	Unit	N	MX	aCV	gM	gCV	MIN	MED	MAX
Ceq	CEQ	ng/mL	12	523.0	0.22	511.0	0.23	372.2	519.0	717.5
Ceq	CL	mL/min	12	167.0	0.23	163.1	0.23	116.2	160.6	223.9
Ceq	CL/BW	mL/min per kg	12	2.40	0.14	2.38	0.14	1.99	2.37	3.20

2P-ANA	2P-10/30	1/1	12	0.330	0.17	0.325	0.19	0.225	0.343	0.406
2P-ANA	2P-15/30	1/1	12	0.452	0.22	0.442	0.22	0.296	0.442	0.642
I-NCA	tmax	h	12	1.77	0.18	n.a.	n.a.	1.25	2.00	2.02
I-NCA	Cmax	ng/mL	12	554.7	0.23	541.0	0.24	374.4	574.2	763.8
I-NCA	CL	mL/min	12	162.0	0.26	157.1	0.26	110.7	151.8	241.4
I-NCA	CL/BW	mL/min per kg	12	2.32	0.17	2.29	0.17	1.77	2.25	3.19
I-NCA	t½	min	12	105.28	0.53	93.57	0.54	40.83	95.70	241.42
PI-Full	tmax	h	12	2.01	0.00	n.a.	n.a.	2.00	2.00	2.02
PI-Full	Cmax	ng/mL	12	539.8	0.22	528.1	0.22	374.4	551.1	725.7
PI-Full	t½	min	12	113.38	0.47	102.90	0.49	40.83	97.27	241.42
PI-short	tmax	h	12	2.01	0.00	n.a.	n.a.	2.00	2.00	2.02
PI-short	Cmax	ng/mL	12	539.8	0.22	528.1	0.22	374.4	551.1	725.7
PI-short	t½	min	12	19.85	0.16	19.65	0.15	16.89	18.73	26.78
FIT-2C	V1	L	12	3.02	0.32	2.90	0.30	1.89	2.62	5.06
FIT-2C	k12	/h	12	0.4373	0.45	0.4048	0.42	0.2060	0.4215	0.9707
FIT-2C	k21	/h	12	0.2499	0.37	0.2319	0.45	0.0777	0.2427	0.4133
FIT-2C	k10	/h	12	3.1878	0.17	3.1438	0.18	2.3756	3.2926	4.2574
FIT-2C	V2	L	12	7.64	1.35	5.06	0.98	1.78	4.28	39.60
FIT-2C	Vdss	L	12	10.67	0.98	8.38	0.71	3.87	7.92	42.77
FIT-2C	t½ (1)	min	12	11.72	0.18	11.55	0.18	8.84	11.18	15.98
FIT-2C	t½ (2)	min	12	232.52	0.65	205.46	0.50	112.13	192.26	685.32
FIT-2C	CL	mL/min	12	156.20	0.25	151.90	0.25	105.52	148.42	242.06
FIT-2C	CL/BW	mL/min per kg	12	2.23	0.14	2.21	0.14	1.83	2.21	2.75

Part B: 2-hour infusion of 15 mg/hour NRL972 (PP; N:12)

METH	Variable	Unit	N	MX	aCV	gM	gCV	MIN	MED	MAX
Ceq	CEQ	ng/mL	12	1394.4	0.258	1354.2	0.256	834.4	1428.4	2275.8
Ceq	CL	mL/min	12	190.1	0.256	184.6	0.256	109.9	175.0	299.6
Ceq	CL/BW	mL/min per kg	12	2.61	0.197	2.56	0.204	1.80	2.64	3.30
2P-ANA	2P-10/30	1/1	12	0.35	0.243	0.34	0.252	0.23	0.35	0.49
2P-ANA	2P-15/30	1/1	12	0.47	0.158	0.46	0.163	0.36	0.48	0.59
I-NCA	tmax	h	12	1.90	0.070	1.90	0.071	1.75	2.00	2.03
I-NCA	Cmax	ng/mL	12	1444.3	0.248	1406.2	0.244	889.6	1463.3	2321.1
I-NCA	CL	mL/min	12	186.9	0.254	181.4	0.260	111.1	174.7	279.5
I-NCA	CL/BW	mL/min per kg	12	2.57	0.211	2.52	0.223	1.72	2.65	3.29
I-NCA	t½	min	12	109.34	0.360	104.45	0.304	76.31	94.00	211.72
PI-Full	tmax	h	12	2.00	0.000	2.00	0.000	2.00	2.00	2.00
PI-Full	Cmax	ng/mL	12	1405.3	0.260	1365.0	0.254	889.6	1401.9	2321.1
PI-Full	t½	min	12	103.48	0.243	101.03	0.225	76.31	94.00	152.27
PI-short	tmax	h	12	2.00	0.000	2.00	0.000	2.00	2.00	2.00
PI-short	Cmax	ng/mL	12	1405.3	0.260	1365.0	0.254	889.6	1401.9	2321.1
PI-short	t½	min	12	20.19	0.110	20.08	0.114	16.22	20.65	23.18
FIT-2C	V1	L	12	3.44	0.172	3.39	0.182	2.37	3.47	4.52
FIT-2C	k12	/h	12	0.2967	0.172	0.2926	0.175	0.2154	0.2967	0.3873
FIT-2C	k21	/h	12	0.3687	0.303	0.3539	0.304	0.2303	0.3460	0.5571
FIT-2C	k10	/h	12	3.2239	0.182	3.1757	0.183	2.4158	3.2487	4.4212
FIT-2C	V2	L	12	3.08	0.471	2.80	0.474	1.50	2.62	6.10
FIT-2C	Vdss	L	12	6.52	0.294	6.28	0.290	3.87	5.84	10.62
FIT-2C	t½ (1)	min	12	12.01	0.168	11.85	0.171	8.60	11.59	15.31
FIT-2C	t½ (2)	min	12	134.90	0.283	129.86	0.298	84.81	132.31	203.05
FIT-2C	CL	mL/min	12	184.3	0.243	179.3	0.250	111.8	172.9	263.9
FIT-2C	CL/BW	mL/min per kg	12	2.54	0.205	2.49	0.216	1.67	2.62	3.37

SAFETY

Wellbeing and adverse events (AEs)

The subjects were hospitalised from the evening of D-1 until the evening of D01 at least 12:00 hours after administration of NRL972. During this time the subjects were under close surveillance in the study clinic.

In Part A (10 mg NRL972 by 2-hour iv infusion), there were no fatal or serious AEs, and none that led to the premature discontinuation of the subject from the study. There were 2 AEs in 1/12 subjects: subject R010 suffered an orthostatic hypotensive and vagal reaction (with faintness and vomiting) when leaving the bed after having been recumbent from at least one hour before until 5 hours after the start of the infusion (2 hours of infusion plus 3 hours of post-infusion profiling); the reaction was self-limiting and regressed readily without intervention other than putting the subject supine with the feet elevated; there were no sequelae. The reaction is judged unlikely to have been related to the investigational medication, but to be due to a prolonged recumbent posture and fasting. In Part B (30 mg NRL972 by 2-hour iv infusion), there were no AEs.

Physical examination

A thorough physical examination took place at SCR and EOT. There were no relevant safety findings at the end of the study compared with the examination at SCR.

Vital functions

Recumbent blood pressure (SBP/DBP) and pulse rate (PR) were recorded at SCR and EOT and before each dosing with NRL972 and at scheduled times after each dosing. There was

no indication of clinically relevant noteworthy average or individual SBP/DBP- or PR-findings over the course of the study that were attributable to the investigational clinical trial medication.

12-lead ECG

A 12-lead digital ECG was recorded at SCR and EOT and at regular times before, during and after each NRL972 infusion. There was no indication of relevant average or individual ECG-findings (HR, PQ, QT, QTc[Bazett], QTc[Fridericia], and QTc[Framingham]: untransformed and changes from baseline) over the course of the study.

Continuous 3-lead ECG HOLTER-recording

A 3-lead ECG was recorded continuously from about one hour before up to 12:00 hours after the start of the infusion; there was no indication of relevant average or individual HOLTER-findings over the course of the study.

CLINLAB: Clinical laboratory tests

Routine safety laboratory testing took place at SCR, prior to NRL972 infusion, at 1:00, 2:00, and 12:00 hours after the start of the infusion and at the EOT. The results were compared with the laboratory defined range of normality. Values outside the range of normality were highlighted and evaluated by the Investigators in terms of their clinical relevance. There were no safety-limiting or noteworthy values.

CONCLUSIONS

- The single iv bolus injection of NRL972-02/2003 (ACPS) led to quantifiable concentrations usually only over the first hour. In the present study, they were quantifiable for a longer time. This resulted in estimates of the late disposition rate (λ_2) that were much slower and more distinct from the earlier faster phase (λ_1).
- This has little implication for the prediction of the magnitude of the equilibrium concentration reached with a protracted iv infusion, since this level relates predominantly to V_1 (central distribution volume) and k_{10} (elimination rate constant), which overall was quite close to λ_1 (rate of the first fast disposition phase). Additionally, the λ_2-phase contributed far less to the total AUC than the λ_1-phase. In contrast this resulted in a distinctly longer time needed to reach equilibrium than predicted.
- In the lower dose group (5 mg/hour NRL972 for two hours) this was not evident for the course of the medians and means, but explains that the concentrations tended to continue to increase during the later phase of the infusion in some subjects.
- In the higher dose group (15 mg/hour NRL972 for two hours) there was no such good agreement between the predictions and the course of the observed medians and means and there was a more general trend that equilibrium had not yet been reached at the end of the 2-hour infusion.
- These distinctions in the expression and capture of the terminal slow disposition phase may have contributed to the apparent lack of dose-proportionality comparing the high with the low dose group. However, the study was not designed to investigate and compare two such groups. Between-group contrasts like the present ones are more likely to be confounded by non-pharmacokinetic group differences in the time courses of the plasma concentrations, particularly since the two groups were not investigated in parallel, but several months apart.
- Two-hour iv infusions of 5 mg/hour (Part A) and 15 mg/hour NRL972 (Part B) were very well tolerated.

29 Oct 2009