2 SYNOPSIS AND TRIAL ABSTRACT

Name of Company: Norgine Ltd. **Name of Active Substance(s):** INN: Fluorescein lisicol tri-sodium salt (SYN: CLF; Code: NRL972)		(For National Authority Use only)

Title: An open study to investigate the effects of chronic viral hepatitis B or C on the pharmacokinetics of cholyl-lysyl-fluorescein (NRL972) before, during and after standard treatment

Norgine Study №: NRL972-09/2008- (CHBC) - EUDRACT-№: 2008-003547-36

Investigators:

- Site BG1: [redacted]
- Site RO1:
- Site RO2:
- Site RO3:
- Site RO4:

Study centre(s):

- Site BG1: Dept. Gastroenterology, UMHAPT "Sveti Ivan Rilski" University Hospital, [redacted] Bulgaria, [redacted]
- [redacted]Site RO1: Emergency County Hospital Cluj Napoca / 2nd Medical Department; [redacted] Romania; [redacted]
- [redacted]Site RO2: Policlinica Algomed; [redacted] RO 300002, Timisoara ; [redacted]
- [redacted]Site RO3: Clinic Institute Fundeni Bucharest, Department of Gastroenterology and Hepatology; [redacted] Romania; [redacted]
- Site RO4: Policlinica Dr. Citu; [redacted] Timisoara, Romania; [redacted]

Note: the trial was also planned to be conducted in Croatia, however no sites were initiated.

Note: the trial was terminated prematurely at site RO4; the data from this site were considered unreliable and are listed, but are not included in the analyses (see section 9.9.2).

Publication (reference):

n.a.

Study period: First screening visit: 23. Mar 2009 Last end-of-trial visit: 30.Sep.2011	**Clinical Phase:** II

GCP-compliance:

The study was planned, conducted, analysed and reported in accordance with the pertinent GCP-Guidelines. Site RO4 was closed prematurely due to a serious breach of GCP.

Objectives of the study:

The trial was conducted to describe and compare the plasma pharmacokinetics of NRL972 after single 15-second i.v. injections of 2 mg NRL972 in patients with chronic viral hepatitis B (CHB) and/or C (CHC) before, during and after treatment for chronic viral hepatitis in

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accordance with the national consensus guidelines (as specifically applicable for each site).

Additionally the safety and tolerability of repeated single i.v. doses of 2 mg NRL972 administered under these conditions was to be described.

Study design:

Multi-national, open-label, within-subject study with repeated single i.v. injections of 2 mg NRL972 on five or seven occasions (for treatments lasting 6 or 12 months respectively) i.e. before, during and after treatment of chronic viral hepatitis in accordance with the national consensus guidelines applicable to the sites of conduct.

Treatment of chronic viral hepatitis:

Patients were to be treated with the medications approved for the treatment of chronic viral hepatitis in accordance with the national consensus guidelines for the reimbursement of such treatment as applicable by country of conduct as detailed in Section 9.4.6.1.

Number of subjects:

Sufficient patients with chronic viral hepatitis B and/or C were to be enrolled to collect at least 6 months of evaluable data in at least 100 patients (minimum: 33 patients with CHB or CHC [combined cases counted as CHC]).

Diagnosis and criteria for inclusion:

Patients with chronic viral hepatitis B (CHB) and/or chronic viral hepatitis C (CHC) eligible for treatment in accordance with the national provisions for reimbursement of such treatment.

- General inclusion criteria:
  - Adult, male or female, age ≥ 18 years and < 65 years
  - Body weight (BW) : 45 - 110 kg
  - Body mass index (BMI) : 18 – 30 $kg.m^{-2}$
  - Confirmed diagnosis of chronic viral hepatitis eligible for treatment of chronic viral hepatitis in accordance with the national consensus guidelines pertinent to the country and site of conduct of the trial and not having been treated for chronic viral hepatitis previously ("de novo" i.e. "naïve")
  - Non-cirrhotic liver disease (on histology within 24 months before screening visit)
  - HIV-Ab negative
  - Willing and able to provide informed consent
- For CHB-patients there were the following specific criteria for inclusion:
  - HBV Serology: HBsAg+ for at least 6 months (at the time of application for treatment)
  - Serum ALAT ≥ 1.5 times ULN for at least 6 months (at the time of application for treatment), but ALAT < 10 times ULN
  - Positive liver biopsy within 24 months before screening visit with signs of active disease (any level of activity by Knodell, METAVIR or ISHAK)
  - HBV DNA counts by quantitative PCR: ≥ 20,000 IU/mL
- For CHC-patients there were the following specific criteria for inclusion:
  - HCV-Ab+ for at least 6 months (at the time of application for treatment)
  - HCV RNA counts by quantitative PCR assay > 10,000 U/mL within the last 6 months (at the time of application for treatment)
  - Positive liver biopsy within 24 months before application for treatment with signs of fibrotic disease (levels of fibrosis METAVIR ≥ F1 or ISHAK ≥ F2)

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- ALAT < 10 times ULN

- For both study groups, the following general exclusion criteria applied:
  - Previous participation in the trial
  - Participation in any other clinical trial within 30 days of entry to this protocol
  - Treatment with any investigational drug within 30 days of entry to this protocol
  - Non-response to previous treatment for chronic viral hepatitis
  - Relapse after previous treatment for chronic viral hepatitis
  - Any other known cause of liver disease other than chronic viral hepatitis B and/or C, including but not limited to hepatitis D, haemochromatosis, alpha$_1$-antitrypsin deficiency, Wilson's disease, autoimmune hepatitis, drug-related liver disease
  - Evidence of advanced liver disease, such as history or presence of ascites, bleeding varices, encephalopathy
  - Patients with organ transplants
  - Hypersensitivity to prospective treatment
  - Any relevant co-morbidity, for instance, but not limited to: limiting uncompensated psychiatric condition (e.g. severe depression, or a history of severe psychiatric disorder), CNS trauma or seizure disorder requiring medication, significant cardiovascular dysfunction within the past 6 months (e.g. angina, congestive cardiac failure, recent myocardial infarction, severe hypertension or significant arrhythmia), patients with an ECG showing clinically significant abnormalities, poorly controlled diabetes mellitus, patients on haemodialysis
  - Daily use of > 40 g alcohol
  - Positive alcohol test at screening-visit
  - Evidence or suspicion of social drug abuse
  - Positive drug test at screening-visit
  - Use of prohibited medication
  - Suspicion or evidence that the subject is not trustworthy and reliable
  - Suspicion or evidence that the subject is not able to make a free consent or to understand the information in this regard.
- Additionally, several criteria were to be considered as reasons to exclude patients from treatment of chronic hepatitis (and hence from participation in the trial)
  - Relevant clinical laboratory test abnormalities, for instance, but not limited to: haemoglobin (Hgb) <11 g dL^{-1} for women and <13 g dL^{-1} for men, WBC count < 3.0 10^9/mL, granulocyte count < 1.5 10^9/mL, lymphocyte count < 0.5 10^9/mL, platelet count < 75 10^9/mL, prothrombin time – INR > 1.4, serum bilirubin > 25 μmol/L (except in functional hyperbilirubinaemia), albumin < 35 g/L, serum creatinine > 133 μmol/L, fasting blood glucose > 7.4 mmol/L for non-diabetic patients, HbA1c > 7% for diabetic patients, positive auto-immune antibodies, TSH outside the normal range (for patients intended for interferon)
  - Relevant co-morbidity, for instance, but not limited to: limiting uncompensated chronic pulmonary disease (e.g. chronic obstructive pulmonary disease), any medical condition requiring, or likely to require during the course of the study, chronic systemic administration of steroids, gout (for patients intended for interferon), immunologically

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mediated disease (e.g. inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune haemolytic anaemia, scleroderma, severe psoriasis, cryoglobulinaemia with vasculitis) – (for patients intended for interferon), patients with clinically significant retinal abnormalities – (for patients intended for interferon)

- Exclusion criteria for all female patients: positive pregnancy test; lactating; not using medically appropriate contraception and/or not willing to maintain such contraception during the treatment of chronic viral hepatitis and up to 6 months thereafter

Test product, dose, batch N°:

Cholyl-L-lysine-fluorescein (SYN: CLF, Code: NRL972), Norgine Ltd., solution for i.v. injection (2 mg NRL972 in 5 mL solution for injection), administered by 15-second i.v. injection for each test i.e. on up to seven occasions (baseline, M03, M06, M09, M12, P03, P06) at an interval of approximately three months between consecutive tests
IMP Batch-N°: NOR-p004

Reference product, batch N°:

Not applicable

Duration of treatments:

The treatment of chronic viral hepatitis lasted up to 12 months (depending on the viral genotype in CHC) but was usually to be stopped earlier in the event of inadequate response. NRL972-tests were to be performed at baseline before the start of the treatment of hepatitis and every three months during treatment for chronic viral hepatitis additionally, follow-up tests were scheduled 3 and 6 months after the end of the treatment of hepatitis.

Schedule:

The patients were to be investigated according to following schedule:

- SCR: screening visit and eligibility assessment: 30 to 2 days before baseline
- BL: baseline evaluation within one month before starting treatment of chronic viral hepatitis
- The third month of treatment (M03) and sixth month (M06) (and if applicable the ninth and twelfth monthsM09, M12)
- Post treatment 3 and 6 months after ending treatment for chronic viral hepatitis (P03, P06)
- The end-of-trial (EOT) evaluation was generally scheduled at P06; a further safety follow-up (SFU) was to be planned for in the event of unresolved safety findings at EOT

At each visit, the following main tests and procedures were to be carried out:

- Wellbeing and adverse events
- Use of medication for treatment of chronic viral hepatitis, use of co-medication and use of medication for AE since the last visit
- Physical examination
- Lead signs and symptoms
- Abdominal ultrasound
- Viraemia by real-time PCR
- Safety clinical laboratory tests
- NRL972-testing (15-second iv injection of 2 mg NRL972 with PK-profiling in plasma up to 1

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hour after dosing and urinary PK-profiling up to 4 hours after dosing)

- Vital signs before and during the NRL972-test

At visits baseline, M06, M12 (if applicable) and P06 the following further tests were to be carried out:

- Special clinical laboratory tests: Serum bile acids, IgG, IgM, IgA, C-reactive protein, iron, transferrin, transferrin saturation (calculated), ferritin, haptoglobin, α_2-macroglobuline, hyaluronic acid, Human N-terminal procollagen III propeptide (PIIINP), apoliprotein A1
- Disease staging: ASAT/ALAT-ratio, APRI-score, HALT-C score, FORNS-index, FIB-4 score, HUI-score, GUCI-index, Fibro-index, HEPASCORE, FibroTest score regression coefficient

CLINICAL PHARMACOLOGY FINDINGS

Subject disposition:

- 143 patients were screened for enrolment (CHB: 34; CHC: 109). Nineteen were not enrolled – reasons of non-eligibility are discussed in the report
- 124 patients were enrolled (CHB: 26; CHC: 98); 92 patients completed the study up to follow-up visit P06; this includes 10 CHC-patients who stopped treatment after six months and one CHC patient who stopped after nine months due to insufficient response.
- 32 patients were discontinued prematurely from the trial either on their own decision or by investigator decision: 23 patients (CHB: 5; CHC: 18) withdrew consent, 5 were lost to follow-up(CHB: 1; CHC:4), 3 were discontinued due to other reasons (CHC:3) and one was discontinued due to a SAE (severe life-threatening anaemia, CHC).

	CHC-patients					CHB-patients				
	BG1	**RO1**	**RO2**	**RO3**	**TOTAL**	**BG1**	**RO1**	**RO2**	**RO3**	**TOTAL**
Screened	27	38	31	13	109	9	2	19	4	34
Enrolled	22	32	31	13	98	8	1	14	3	26
M03	21	28	29	13	91	8	1	13	3	25
M06	21	26	28	12	87	8	0	13	3	24
M09	17	21	24	9	71	8	0	13	3	24
M12	16	21	23	7	67	8	0	13	3	24
P03	21	22	25	9	77	8	0	12	3	23
P06	19	20	24	9	72	8	0	9	3	20
DISC*	3	12	7	4	26	0	1	5	0	6
M06>P03**	4	1	3	2	10	0	0	0	0	0
M09>P03***	1	0	0	0	1	0	0	0	0	0

*DISC: discontinued
**M06>P03: patients who progressed directly to P03 while treatment was discontinued after M06
**M09>P03: patient who progressed directly to P03 while treatment was discontinued after M06

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Demographics

All enrolled patients were Caucasian; the descriptive statistics (mean ± SD and range; numbers by gender and total) of the main demographic features were as follows:

Criterion	CHB	CHC
Number - total	26	98
Number - females	9	59
Number - males	17	39
Age (years)	40 ± 13 (19 - 63)	47 ± 12 (18 - 65)
Body Weight (kg)	74 ± 14.8 (54 - 100)	72 ± 11.9 (46.8 - 103.3)
BMI (kg/m^2)	24.93 ± 3.88 (18.2 - 30.07)	25.14 ± 2.98 (18.28 - 30.45)

BASELINE AND BACKGROUND FEATURES

Diagnosis & aetiology

All patients were diagnosed with chronic viral hepatitis with the date of diagnosis between 1977 and 2009 (CHB) and between 1980 and 2009 (CHC). Two of the CHC-patients also proved positive for HBs-Ag (active mixed infection). All diagnoses were confirmed by virology and serology testing.

All patients were considered eligible for standard treatment in accordance with the national consensus guidelines. All but 7 patients had been admitted in the national reimbursement program for the treatment of chronic viral hepatitis.

Genotype

95 CHC-patients had a genotype 1 HCV-infection, only 3/98 had genotype 3; no other genotypes were represented.

Biopsy

Most (122) patients had baseline biopsy findings (within 24 months before screening); 81% of patients had a METAVIR activity score ≥ 2 and 79% had a METAVIR fibrosis score ≥ 2.

Serology

None of the patients was HIV-positive.

None of the 22 tested CHC-patients and none of the 8 tested CHB-patients proved positive for anti-HAV IgM-antibodies, although 10/22 CHC-patients and 5/8 tested CHB-patients proved positive for older type antibodies.

All of the CHC-patients tested positive for anti-HCV antibodies; two of the CHC-patients also proved positive for HBs-Ag (active mixed infection), whereas 24/97 tested CHC-patients were positive for anti-HBs, 12/97 for anti-HBe antibodies, and 4/22 tested CHC-patients for anti-HBc total antibodies. All of the CHB-patients tested positive for HBs-Ag, 9/26 also for HBe-Ag and 18/26 for anti-HBe antibodies, but none for anti-HBs.

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Virology

77% and 99% of the CHB- and CHC-patients had a baseline PCR viraemia of at least 10,000 IU/mL. The percent patients enrolled by categorised log(viraemia) is summarised in the following table:

	log(viraemia) categories											
CHB	**0.00**	**(0-1]**	**(1-2]**	**(2-3]**	**(3-4]**	**(4-5]**	**(5-6]**	**(6-7]**	**(7-8]**	**(8-9]**	**(9-10]**	**MD***
SCR	0.0	0.0	3.8	0.0	19.2	3.8	19.2	11.5	23.1	15.4	3.8	0.0
M03	19.2	0.0	15.4	3.8	23.1	3.8	11.5	7.7	11.5	0.0	0.0	3.8
M06	19.2	0.0	7.7	26.9	15.4	11.5	3.8	3.8	0.0	3.8	0.0	7.7
M09	26.9	0.0	19.2	11.5	7.7	11.5	3.8	7.7	3.8	0.0	0.0	7.7
M12	26.9	0.0	3.8	15.4	19.2	11.5	7.7	3.8	3.8	0.0	0.0	7.7
P03	19.2	0.0	3.8	15.4	23.1	11.5	3.8	7.7	3.8	0.0	0.0	11.5
P06	15.4	0.0	3.8	15.4	15.4	11.5	3.8	0.0	7.7	3.8	0.0	23.1
	log(viraemia) categories											
CHC	**0.00**	**(0-1]**	**(1-2]**	**(2-3]**	**(3-4]**	**(4-5]**	**(5-6]**	**(6-7]**	**(7-8]**	**(8-9]**	**(9-10]**	**MD***
SCR	0.0	0.0	0.0	0.0	1.0	17.3	39.8	37.8	4.1	0.0	0.0	0.0
M03	64.3	0.0	9.2	6.1	2.0	5.1	4.1	3.1	0.0	0.0	0.0	6.1
M06	74.5	0.0	1.0	1.0	3.1	0.0	6.1	3.1	0.0	0.0	0.0	11.2
M09	66.3	0.0	2.0	0.0	2.0	1.0	1.0	1.0	0.0	0.0	0.0	26.5
M12	63.3	0.0	1.0	0.0	0.0	0.0	3.1	1.0	0.0	0.0	0.0	31.6
P03	44.9	0.0	0.0	1.0	0.0	4.1	17.3	11.2	0.0	0.0	0.0	21.4
P06	40.8	0.0	0.0	0.0	0.0	3.1	16.3	13.3	0.0	0.0	0.0	26.5

*MD: missing data due to discontinuation

Subgroups according to viraemia response

Based on the viraemia data, the patients were assigned to one of the following categories: NE (viraemia response not evaluable), NR (no-response i.e. none of the values reduced to “not detectable”), RE (response, but not evaluable whether sustained), RNS response not sustained up to the last post-treatment visit,, RS (response with sustained response up to the last post-treatment visit). The distribution of the percentage of patients by response category is summarised in the following table:

	CHC-patients (N: 98)					**CHB-patients (N:26)**				
Category	**BG1**	**RO1**	**RO2**	**RO3**	**TOTAL**	**BG1**	**RO1**	**RO2**	**RO3**	**TOTAL**
NE	4.5%	15.6%	9.7%	7.7%	10.2%	0%	100.0%	7.1%	0%	7.7%
NR	13.6%	3.1%	16.1%	23.1%	12.2%	25.0%	0%	42.9%	33.3%	34.6%
RE	0%	15.6%	3.2%	15.4%	8.2%	0%	0%	7.1%	0%	3.8%
RNS	27.3%	18.8%	35.5%	15.4%	25.5%	37.5%	0%	42.9%	33.3%	38.5%
RS	54.5%	46.9%	35.5%	38.5%	43.9%	37.5%	0%	0%	33.3%	15.4%

Lead signs and symptoms

Most of the patients had no objective lead signs. At screening, discrete hepatomegaly was recorded in 5/26 CHB-patients and 16/98 CHC-patients, discrete splenomegaly in 2/26 CHB-patients and in 4/98 CHC-patients. At baseline, discrete hepatomegaly was recorded in 4/26 CHB-patients and 15/98 CHC-patients, discrete splenomegaly in 2/26 CHB-patients and in 1/98 CHC-patients.

Several subjects had some, mostly mild subjective symptomatic impairment. Mild lead symptoms (fatigue; feeling weak/faint; feeling depressed; loss of appetite; nausea; vomiting;

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muscle/joint pain; abdominal pain; liver pain; dark-coloured urine; pale-coloured stools; sexual dysfunction; fever; mood swings; irritability; difficulty concentrating; disturbed orientation) were more prevalent during treatment. On-treatment there also were more patients with moderate symptom intensity; in single patients, symptoms reached "severe" intensity; all symptoms readily returned to the baseline values.

Co-morbidity

The most frequent associated diagnoses were arterial hypertension (CHB: 6/26; CHC: 29/98 patients), post-menopausal complaints (CHB: 0/26; CHC: 29/98 patients) and diabetes mellitus (CHB: 3/26; CHC: 11/98 patients).

Treatment of chronic viral hepatitis

CHC-patients were mostly treated with pegylated interferon plus ribavirin; about 70% of the CHB-patients were treated with interferon (mostly pegylated interferon alpha 2a), but eight patients were treated with entecavir, a novel guideline-compliant treatment which was not (to be) stopped after 12 months.

Co-medication

14/26 (54%) CHB-patients and 57/98 (58%) CHC-patients reported the use of medication at screening (including the 4 weeks before screening). There was frequent use of medication for AEs on- and after-treatment of chronic hepatitis : 24 of the 26 enrolled CHB-patients suffered at least one AE; in 18 of these, medication was used to alleviate the AE (use of medication reported in 83/449 AE-records). 91 of the 98 enrolled CHC-patients suffered at least one AE; in 60 of these, medication was used to alleviate the AE (use of medication recorded in 197/1887 AE-records). This mostly related to headache, abdominal pain, liver pain, and fever.

Clinical laboratory testing

In CHB-patients, the treatment of chronic viral hepatitis was associated with a decrease in haemoglobin (M06 & M12), white blood cells (M06 & M12), absolute granulocyte (M06) and lymphocyte (M06 & M12) and platelet counts (M06); additionally, there was a mean decrease in serum bilirubin (M06 & M12), ALAT (M06 & M12), ASAT (M12), and alkaline phosphatase (M06 & M12). At P06 relative to M12, there was a trend of an increase in white blood cells and the absolute granulocyte count, but his recovery was more distinct for the absolute lymphocyte count and haemoglobin. There were no relevant changes at P06 relative to M12 with regard to serum bilirubin, ASAT, ALAT, and alkaline phosphatase.

In CHC-patients, the treatment of chronic viral hepatitis was associated with a decrease in haemoglobin (M06 & M12) with a rise in the mean corpuscular cell volume (MCV) (M06 & M12), a decrease in white blood cells (M06 & M12), absolute granulocyte (M06 & M12) and lymphocyte (M06 & M12) and platelet counts (M06 & M12)); additionally, there was a slight mean decrease in glucose (M06), total protein (M06 & M12), albumin (M12), creatinine (M12), bilirubin (M12), and total cholesterol (M06 & M12), whereas there was a more distinct decrease in the mean serum ASAT (M06 & M12), ALAT (M06 & M12), g-GT (M06 & M12) and a slight decrease in creatinine phosphokinase (M06 & M12) and potassium levels (M06 & M12). At P06 relative to M12, there was an increase in haemoglobin with a decrease in MCV, an increase in WBC, absolute granulocyte, lymphocyte and platelet count, and also there was recovery of the average decrease in total protein, albumin and cholesterol; the mean ASAT, ALAT, g-GT, alkaline phosphatase, creatinine phosphokinase, and potassium levels tended to rise again.

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Special laboratory tests

At baseline the mean transferrin and apolipoprotein A1 tended to be lower in the CHB-patients; in contrast, there was a slight trend of a higher mean PIIINP-level compared with the CHC-patients.

On-study, in CHB-patients the mean ferritin level was higher at M06 relative to baseline; a similar – albeit smaller – trend was seen at M012; this was associated with lower mean iron levels and lower transferrin saturation. At P06 (relative to M12), mean iron levels were higher again, whereas there were trends of lower mean ferritin and higher transferrin levels.

On-study, in CHC-patients, there were lower bile acid levels (M12), lower mean iron (M12) and transferrin levels (M12), lower mean apolipoprotein A1 (M06 & M12), lower IgM (M12), higher mean ferritin (M06 & M12), and hyaluronic acid levels (M06) relative to baseline. At P06 relative to M12, there were higher mean iron levels, higher mean transferrin levels, and higher mean apolipoprotein A1 levels, such that the changes observed on treatment for chronic viral hepatitis appeared to regress once the treatment was stopped.

Abdominal ultrasound

The mean pre-treatment estimated liver volume ("volume-3" – Section 9.6.3) was 2497 ± 734 mL (range: 1057 to 3769) and 2101 ± 788 mL (range: 673 to 4074 mL) in CHB- and CHC-patients, respectively. On-study there was no relevant change in liver volume.

No ascites was detected in any of the patients. 7 and 2 CHB-patients had mild and moderate fatty infiltration at baseline; 21 and 2 CHC-patients had had mild and moderate fatty infiltration at baseline.

Doppler ultrasound

Findings at baseline:

- Hepatic arterio-venous flow: the portal venous flow was open in all subjects; in all, but one subject the portal venous flow velocity was normal; in all, but one subject the portal venous flow was reported to be hepatopetal
- The hepatic arterial stream was open in all patients
- Collaterals: collaterals were reported in only one patient in whom porto-systemic collaterals, collaterals of the umbilical vein and splenic-renal shunts were reported

Findings on-study:

There were no relevant changes over the course of the study.

Disease scores/indices

The descriptive statistics of the mean findings (mean ± SD; range) for the various disease scores/indices for the main visits (baseline, M06, M12, P06) are summarised in the following:

Disease scores/indices: CHB-patients

	BL	M06	M12	P06
N	26	24	24	20
AST/ALT	0.66 ± 0.25 (0.36 - 1.34)	0.83 ± 0.33 (0.49 - 2.06)	0.9 ± 0.34 (0.42 - 1.75)	0.92 ± 0.36 (0.42 - 1.57)
APRI	0.79 ± 0.66 (0.2 - 3.4)	0.85 ± 0.5 (0.15 - 2.2)	0.55 ± 0.38 (0.14 - 1.81)	0.4 ± 0.22 (0.16 - 1)

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HALT-C	0.29 ± 0.15 (0.08 - 0.68)	0.42 ± 0.17 (0.12 - 0.8)	0.38 ± 0.19 (0.12 - 0.72)	0.34 ± 0.18 (0.14 - 0.78)
FORNS	3.66 ± 2.04 (-0.61 - 8.56)	5.16 ± 2.29 (0.96 - 10.07)	4.56 ± 2.56 (0.4 - 9.93)	3.89 ± 1.79 (0.35 - 7.5)
FIB-4	1.58 ± 1.19 (0.29 - 6.27)	1.96 ± 1.14 (0.37 - 4.81)	1.53 ± 1.05 (0.27 - 4.52)	1.22 ± 0.59 (0.38 - 2.5)
HUI	0.132 ± 0.169 (0.003 - 0.635)	0.24 ± 0.245 (0.007 - 0.774)	0.19 ± 0.231 (0.002 - 0.784)	0.148 ± 0.156 (0.005 - 0.517)
GUCI	0.878 ± 0.776 (0.212 - 3.981)	0.89 ± 0.495 (0.135 - 2.05)	0.589 ± 0.385 (0.139 - 1.795)	0.438 ± 0.257 (0.165 - 1.073)
Fibro-Index	1.49 ± 0.56 (0.54 - 3.2)	1.89 ± 0.47 (1.15 - 2.8)	1.78 ± 0.52 (0.78 - 2.74)	1.41 ± 0.48 (0.62 - 2.17)
HEPASCORE	0.57 ± 0.27 (0.17 - 0.99)	0.62 ± 0.26 (0.17 - 0.99)	0.57 ± 0.28 (0.14 - 0.96)	0.56 ± 0.23 (0.24 - 0.9)
FIBROTEST	-0.124 ± 1.28 (-2.192 - 2.453)	-0.038 ± 1.495 (-2.279 - 2.826)	0.078 ± 1.549 (-2.329 - 3.038)	-0.128 ± 1.224 (-1.796 - 1.865)

In CHB-patients there was an increase in the mean ASAT/ALAT-ratio, the mean HALT-C score, the mean FORNS-index, and the mean Fibro-index at M06 relative to baseline. At M12, there were similar trends, but they were less distinct, except for the ASAT/ALAT-ratio. At P06, there was little change from M12 except for the Fibro-index which was decreased relatively from M12. However, overall these trends were rather weak.

Disease scores/indices: CHC-patients

	BL	**M06**	**M12**	**P06**
N	98	87	67	72
AST/ALT	0.73 ± 0.26 (0.37 - 1.96)	1.35 ± 0.49 (0.56 - 2.84)	1.25 ± 0.49 (0.31 - 3.07)	1.12 ± 0.47 (0.38 - 3.13)
APRI	0.78 ± 0.64 (0.13 - 3.58)	0.61 ± 0.44 (0.11 - 2.61)	0.5 ± 0.57 (0.11 - 4.63)	0.49 ± 0.55 (0.07 - 3.19)
HALT-C	0.28 ± 0.2 (0.01 - 1)	0.54 ± 0.22 (0.1 - 1)	0.47 ± 0.21 (0.09 - 0.97)	0.36 ± 0.23 (0.02 - 0.99)
FORNS	4.67 ± 1.85 (-0.7 - 8.94)	5.41 ± 1.91 (0.09 - 10.05)	5.01 ± 1.91 (0.73 - 9.7)	4.04 ± 1.93 (-0.91 - 8.77)
FIB-4	1.8 ± 1.13 (0.26 - 5.38)	1.84 ± 1.14 (0.26 - 6.38)	1.59 ± 1.06 (0.33 - 7.49)	1.41 ± 0.99 (0.2 - 5.45)
HUI	0.1 ± 0.124 (0 - 0.551)	0.18 ± 0.187 (0 - 0.813)	0.137 ± 0.157 (0.001 - 0.666)	0.099 ± 0.135 (0 - 0.606)
GUCI	0.887 ± 0.847 (0.135 - 4.873)	0.685 ± 0.578 (0.113 - 3.76)	0.564 ± 0.758 (0.122 - 6.252)	0.549 ± 0.684 (0.064 - 4.277)
Fibro-Index	1.42 ± 0.59 (-0.54 - 2.8)	1.8 ± 0.51 (0 - 2.73)	1.59 ± 0.47 (0.46 - 3.04)	1.25 ± 0.54 (-0.56 - 2.79)
HEPASCORE	0.51 ± 0.31 (0.04 - 1)	0.62 ± 0.3 (0.05 - 1)	0.52 ± 0.29 (0.08 - 1)	0.45 ± 0.29 (0.08 - 1)
FIBROTEST	-0.029 ± 1.483 (-2.715 - 3.751)	0.228 ± 1.706 (-2.866 - 4.54)	-0.249 ± 1.474 (-3.09 - 3.407)	-0.469 ± 1.363 (-2.895 - 3.456)

Name of Company: Norgine Ltd. **Name of Active Substance(s):** INN: Fluorescein lisicol tri-sodium salt (SYN: CLF; Code: NRL972)		(For National Authority Use only)

In CHC-patients, with a larger number of observations, there were more distinct differences: there were increases in the mean ASAT/ALAT-ratio (M06 & M12), mean HALT-C score (M06 & M12), mean FORNS-index (M06), mean HUI-score (M06), mean Fibro-index(M06 & M12), and mean HEPASCORE (M06), whereas there was a decrease in the mean APRI-score (M06 & M12). At P06 relative to M12, there was a decrease in the mean HALT-C, mean FORNS-index, and the mean Fibro-index, whereas the mean ASAT/ALAT-ratio remained relatively high and the APRI-score relatively low (compared with baseline).

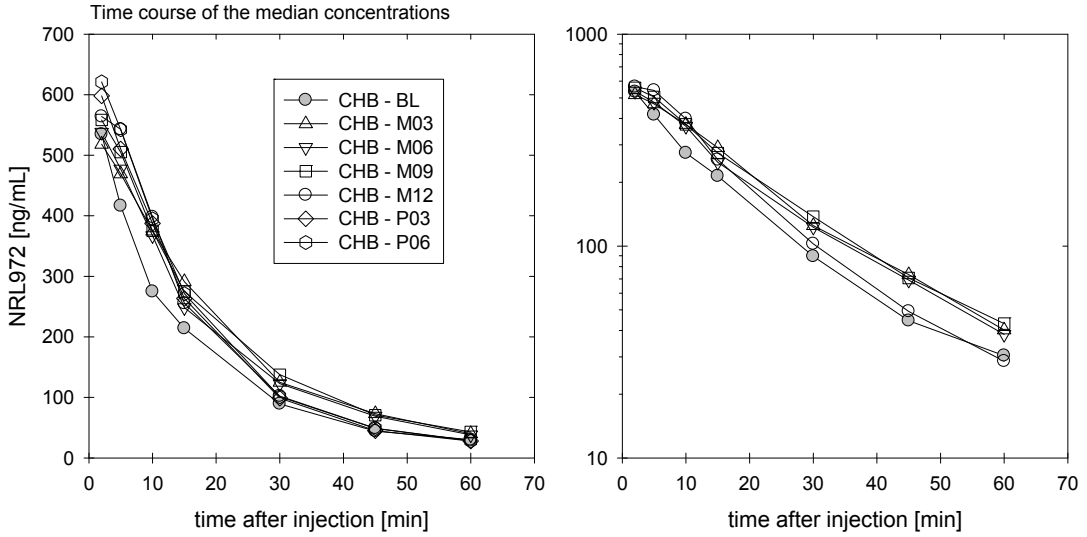
PHARMACOKINETICS OF NRL972

Not all PK-profiles were well evaluable; some profiles were to be discarded from further analysis due to presumed paravenous injection of NRL972 (5 profiles), too high pre-dose concentrations (5 profiles), presumed sample contamination (6 profiles), and noteworthy loss of smoothness of the post-dosing decline (7 profiles).

PHARMACOKINETICS OF NRL972 – CHB-patients

Time courses of the plasma concentrations

The time courses of the median plasma concentrations of NRL972 over the course of the study (during and after treatment of chronic viral hepatitis) are presented in the following graph (left: linear axis; right: log-linear axis):



Plasma pharmacokinetics of NRL972

The descriptive statistics of the main PK-criteria for the main visits (baseline, M06, M12, and P06) are detailed in the following table:

		BL	M06	M12	P06
		26	23	23	20
C(30):C(10)	[1/1]	0.331 ± 0.13 (0.158 - 0.659)	0.386 ± 0.125 (0.146 - 0.621)	0.316 ± 0.12 (0.124 - 0.593)	0.274 ± 0.105 (0.11 - 0.476)
C(30):C(15)	[1/1]	0.457 ± 0.149 (0.228 - 0.763)	0.536 ± 0.178 (0.247 - 1.016)	0.445 ± 0.14 (0.23 - 0.752)	0.39 ± 0.115 (0.183 - 0.618)

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C(45):C(15)		[1/1]	0.246 ± 0.133 (0.093 - 0.571)	0.305 ± 0.134 (0.134 - 0.633)	0.229 ± 0.107 (0.079 - 0.475)	0.194 ± 0.083 (0.093 - 0.373)
2P1[1]	t1/2	min	13.6 ± 6.4 (7.5 - 33.2)	15.5 ± 5.8 (7.2 - 29.1)	12.7 ± 5 (6.7 - 26.5)	11.2 ± 3.8 (6.3 - 20.2)
2P1	C0	ng/mL	547.7 ± 184.2 (126 - 922)	594.7 ± 121.3 (362 - 807.1)	676.9 ± 175.5 (361.5 - 1047.8)	747.2 ± 190.9 (490.7 - 1083.4)
2P1	CL/BW	mL/(min *kg)	3.28 ± 1.44 (0.86 - 6.37)	2.42 ± 1.01 (1.06 - 4.91)	2.6 ± 0.85 (0.91 - 4.41)	2.53 ± 0.88 (1.13 - 4.21)
2P2[2]	t1/2	min	15.8 ± 7.2 (8.8 - 37.2)	18.8 ± 8.6 (10.4 - 45.4)	14.3 ± 5.1 (8.2 - 27.9)	12.9 ± 3.6 (8.7 - 21.1)
2P2	C0	ng/mL	473.4 ± 172.7 (122.2 - 792.2)	525.1 ± 161.5 (134.4 - 758.1)	609.2 ± 176.5 (324 - 894)	618 ± 170.2 (357.8 - 1036.9)
2P2	CL/BW	mL/(min *kg)	3.43 ± 1.77 (0.83 - 7.72)	2.55 ± 1.64 (1.04 - 8.62)	2.58 ± 0.79 (0.97 - 3.86)	2.68 ± 1.07 (1.15 - 5)
NCA[3]	Cmax	min	547.3 ± 142.5 (322 - 934)	587.2 ± 146.4 (414 - 1079)	627.6 ± 139 (416 - 1002)	643.5 ± 138.5 (443 - 886)
NCA	t1/2	ng/mL	17.3 ± 7.4 (8.8 - 35.3)	19.4 ± 8.2 (7.3 - 45.7)	16.5 ± 5.7 (6.7 - 35.1)	15 ± 3.9 (8.7 - 22.6)
NCA	CL/BW	mL/(min *kg)	3.29 ± 1.54 (0.81 - 6.72)	2.41 ± 1.08 (1.01 - 5.03)	2.65 ± 0.88 (0.94 - 4.7)	2.61 ± 0.96 (1.14 - 4.63)
F1C[4]	t1/2	min	14.3 ± 5.5 (8.3 - 31.2)	16.8 ± 6.5 (6.9 - 30.2)	14 ± 5 (6.3 - 28.8)	12.8 ± 3.9 (7.9 - 21.2)
F1C	C0	ng/mL	534 ± 147.3 (254 - 874.6)	585.4 ± 109.7 (411.1 - 816.1)	629.1 ± 129.3 (392.6 - 923.3)	670.6 ± 155.8 (480.8 - 1011.3)
F1C	CL/BW	mL/(min *kg)	3.06 ± 1.36 (0.82 - 6.1)	2.28 ± 0.96 (1.03 - 4.54)	2.48 ± 0.79 (0.95 - 4.19)	2.43 ± 0.86 (1.11 - 4.38)
URINE	Ae [0-4]	ng	6696 ± 6015 (575 - 25694)	9186 ± 8752 (726 - 41503)	8262 ± 7779 (2358 - 40930)	6921 ± 5198 (1760 - 25526)

[1] 2P1 - Two-Point Analysis Based On The Concentrations At 30 And 10 Minutes After Injection
[2] 2P2 - Two-Point Analysis Based On The Concentrations At 45 And 15 Minutes After Injection
[3] NCA – Non Compartmental Analysis
[4] F1C - One-Compartment Mono-Exponential Fit

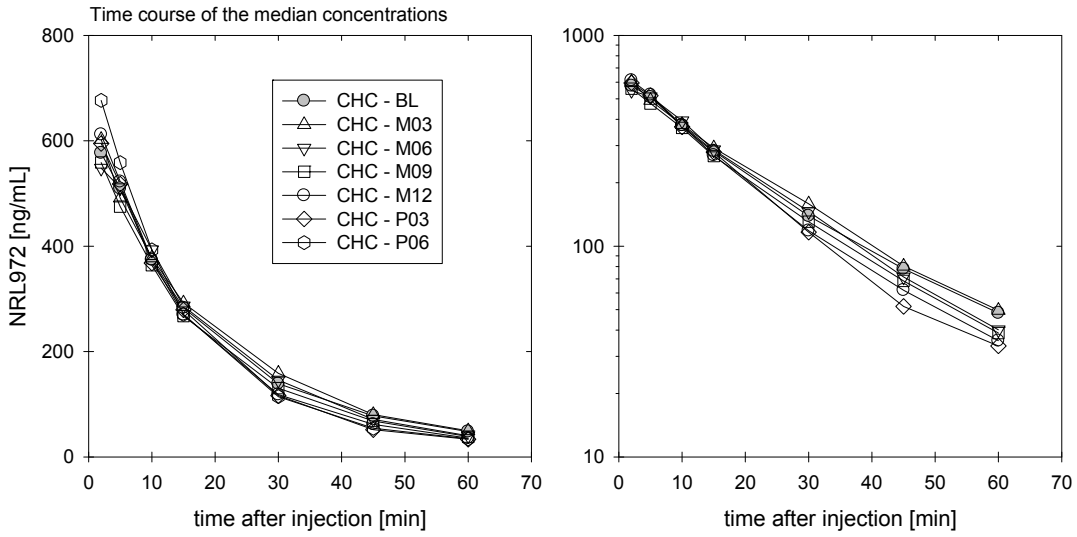
In CHB-patients, there was a slightly longer NRL972 t½ and distinctly lower clearance (irrespective of the method used) at M06 relative to BL; at M12 there was a similar, but less distinct trend. Additionally, at M12, Cmax and C0 tended to be higher. There was little difference between P06 and M12.

PHARMACOKINETICS OF NRL972 – CHC-patients

Time courses of the plasma concentrations

The time courses of the median plasma concentrations of NRL972 over the course of the study (during and after treatment of chronic viral hepatitis) are presented in the following graph (left: linear axis; right: log-linear axis):

Name of Company: Norgine Ltd. **Name of Active Substance(s):** INN: Fluorescein lisicol tri-sodium salt (SYN: CLF; Code: NRL972)		(For National Authority Use only)



Plasma pharmacokinetics of NRL972

The descriptive statistics of the main PK-criteria for the main visits (baseline, M06, M12, and P06) are detailed in the following table:

			BL	M06	M12	P06
		N:	89	85	66	72
C(30):C(10)		[1/1]	0.408 ± 0.133 (0.194 - 0.796)	0.398 ± 0.131 (0.137 - 0.765)	0.338 ± 0.119 (0.134 - 0.73)	0.332 ± 0.152 (0.095 - 0.769)
C(30):C(15)		[1/1]	0.539 ± 0.136 (0.283 - 0.851)	0.51 ± 0.132 (0.235 - 0.867)	0.454 ± 0.125 (0.224 - 0.833)	0.458 ± 0.158 (0.191 - 0.867)
C(45):C(15)		[1/1]	0.321 ± 0.14 (0.113 - 0.744)	0.291 ± 0.126 (0.077 - 0.685)	0.242 ± 0.108 (0.078 - 0.652)	0.246 ± 0.148 (0.077 - 0.705)
2P1[1]	$t_{1/2}$	min	17 ± 8.5 (8.4 - 60.6)	16.5 ± 7.9 (7 - 51.7)	13.6 ± 5.6 (6.9 - 44.1)	14.2 ± 8.8 (5.9 - 52.8)
2P1	C0	ng/mL	617.6 ± 187.8 (211.5 - 1004)	627.6 ± 160.7 (331 - 1092.2)	664.7 ± 195.3 (324.7 - 1301.5)	732.2 ± 198.8 (269.2 - 1350.2)
2P1	CL/BW	mL/(min* kg)	2.4 ± 1.39 (0.39 - 10.78)	2.4 ± 0.95 (0.56 - 5.38)	2.8 ± 1.17 (0.74 - 6.29)	2.48 ± 1.22 (0.51 - 6.41)
2P2[2]	$t_{1/2}$	min	19.9 ± 9.9 (9.6 - 70.2)	17.9 ± 8.1 (8.1 - 54.9)	15.3 ± 6.3 (8.2 - 48.6)	16.2 ± 9.5 (8.1 - 59.6)
2P2	C_0	ng/mL	534.5 ± 182.8 (87.3 - 1073.6)	574.2 ± 149.5 (287.1 - 1011.6)	602.1 ± 196.1 (144.9 - 1285.2)	633.3 ± 209.2 (116.4 - 1477.7)
2P2	CL/BW	mL/(min* kg)	2.44 ± 1.33 (0.34 - 7.42)	2.41 ± 0.98 (0.53 - 5.37)	2.82 ± 1.34 (0.69 - 8.33)	2.65 ± 1.52 (0.46 - 9.24)
NCA[3]	C_{max}	min	626.5 ± 217.5 (218.6 - 1931)	582.4 ± 134.6 (306.1 - 910)	622.6 ± 160.7 (326.3 - 1002)	700.1 ± 169.5 (335 - 1091)
NCA	$t_{1/2}$	ng/mL	24.1 ± 15 (10.1 - 104.2)	20.1 ± 9 (8.1 - 56)	16.3 ± 6.2 (7.2 - 50.5)	19.2 ± 11.4 (6 - 67)
NCA	CL/BW	mL/(min* kg)	2.28 ± 1.06 (0.29 - 6.68)	2.41 ± 0.97 (0.54 - 4.89)	2.86 ± 1.28 (0.68 - 7.3)	2.49 ± 1.22 (0.43 - 5.01)

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F1C[4]	$t_{1/2}$	min	18.3 ± 8.4 (8.7 - 63.5)	17.8 ± 8.3 (7.8 - 57.1)	14.5 ± 5.6 (6.9 - 46.8)	15.5 ± 8.9 (5.5 - 57.9)
F1C	C_0	ng/mL	602.2 ± 171.5 (219.4 - 1162.1)	601.3 ± 142 (317.8 - 946.6)	644 ± 170.7 (321.9 - 1081)	695.2 ± 170.1 (334.3 - 1042.2)
F1C	CL/BW	mL/(min* kg)	2.18 ± 0.97 (0.36 - 6.06)	2.29 ± 0.88 (0.53 - 4.5)	2.68 ± 1.14 (0.7 - 6.66)	2.33 ± 1.07 (0.47 - 4.62)
URINE	$Ae_{[0-4]}$	ng	12997 ± 11945 (575 - 67859)	9721 ± 7376 (550 - 47157)	7329 ± 5017 (550 - 24570)	9620 ± 13577 (675 - 100719)

[1] 2P1 - Two-Point Analysis Based On The Concentrations At 30 And 10 Minutes After Injection
[2] 2P2 - Two-Point Analysis Based On The Concentrations At 45 And 15 Minutes After Injection
[3] NCA – Non Compartmental Analysis
[4] F1C - One-Compartment Mono-Exponential Fit

In CHC-patients there was little difference in the pharmacokinetics of NRL972 at M06 compared with baseline, except for a slightly shorter NCA-t½, which was not confirmed for the other t½-estimates. At M12, there were distinct effects on the pharmacokinetics of NRL972: the mean C(30):C(10)- and C(30):C(15)-ratios were lower, the mean t½ was shorter and the mean CL/BW tended to be higher than at baseline. These changes from baseline lasted up to P06 since little difference was seen between the mean pharmacokinetics at P06 and those at M12, except for slightly higher mean Cmax- and C0-values.

Drug-disease interactions

At baseline, for CHB-patients there was no indication of any close correlation between the individual C(30):C(10)-ratios and viraemia, change in viraemia at M06, special laboratory tests, or any of the disease scores/indices.

For CHC-patients, there was a consistent trend that a) viraemia non-responders had higher baseline C(30):C(10)-, C(30):C(15)-, and C(45):C(15)-ratios, slower NRL972 elimination, t½ and lower NRL972-clearance relative to responders and b) that this distinction was already evident at baseline testing. Furthermore, there was a trend that this difference became even larger over the progress of the study, also in the post-treatment phase relative to the patients with sustained response in particular. This shown in the following scatter- and box-&-whiskers plots that present the C(30):C(10)-ratio by visit and viraemia response category:

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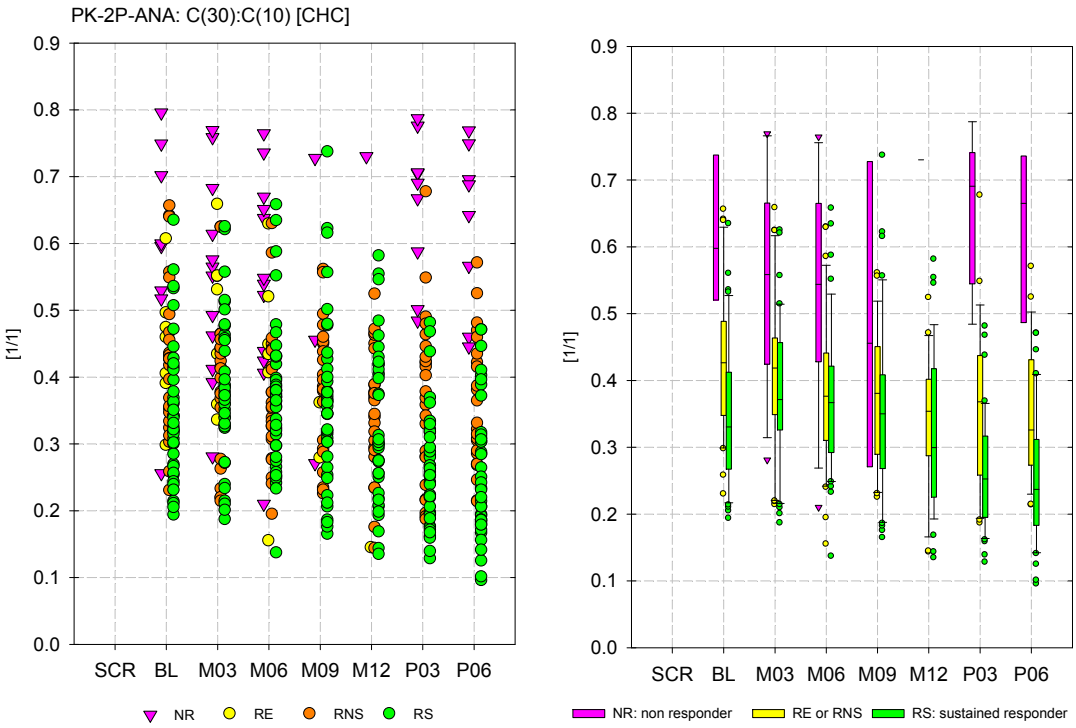

This trend was evident in particular for patients who failed to reach “non-detectable” viraemia at any time on-treatment, but there was a similar – albeit weaker - trend in the group of patients who reached response, but failed to sustain it “RNS”). This is shown below by the descriptive statistics (number of data; mean ± SD; range) of the baseline C(30):C(10)-ratios in the different viraemia response categories..)

ALL	NE	NR	R-ALL	RE	RNS	RS
N: 89	N: 8	N: 8	N: 73	N: 7	N: 25	N: 41
0.41 ± 0.131	0.44 ± 0.12	0.59 ± 0.17	0.38 ± 0.11	0.45 ± 0.10	0.42 ± 0.12	0.35 ± 0.10
(0.19 - 0.80)	(0.21 - 0.57)	(0.26 - 0.80)	(0.19 - 0.66)	(0.30 - 0.61)	(0.23 - 0.66)	(0.19 - 0.63)

ALL: all patients; NE: patients for whom the viraemia response was not evaluable; NR: non-responders; RE: patients who were responders, but for whom it could not be assessed whether the response was sustained; RNS: responders who were shown to fail to sustain the response; RS: responders who were shown to sustain the response; R-all: all patients who were shown to reach “non-detectable viraemia irrespective of whether this response was sustained = RE + RNS + RS

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This distinction in terms of viraemia response was particularly well expressed by means of the pharmacokinetics of NRL972, but this property was not found to be unique to NRL972. Non-responders generally tended to have higher total and direct bilirubin levels; higher ASAT, ALAT and g-GT levels; higher iron levels; higher transferrin saturation levels; higher alpha$_2$-macroglobulin values; higher IgG and IgA levels; a higher APRI-score, FORNS-index, FIB-4 score, GUCI score, HEPASCORE, and FibroTest regression coefficient; shown by the descriptive statistics (number of data; mean ± SD; range) below.

	ALL	**NE**	**NR**	**RE**	**RNS**	**RS**
N:	98	10	12	8	25	43
BILI-t	10.8 ± 5.8 (1.7 - 35.6)	11.2 ± 4.4 (7.2 - 17.8)	15.8 ± 7.1 (7.5 - 35.6)	10.2 ± 4.6 (4.6 - 18.5)	9 ± 4.1 (1.7 - 19.2)	10.5 ± 6.2 (2.7 - 30.4)
BILI-d	4.51 ± 2.11 (0 - 10.26)	5.31 ± 2.21 (2.57 - 8.38)	6.02 ± 2.48 (0 - 8.38)	4.3 ± 0.94 (3.08 - 5.47)	4.11 ± 1.53 (1.71 - 7.87)	4.17 ± 2.26 (0.3 - 10.26)
AST	63 ± 36 (22 - 215)	60 ± 30 (34 - 137)	86 ± 50 (43 - 215)	50 ± 22 (25 - 82)	68 ± 37 (29 - 159)	58 ± 31 (22 - 172)
ALT	90 ± 45 (23 - 298)	95 ± 41 (57 - 170)	99 ± 40 (32 - 154)	70 ± 28 (39 - 121)	84 ± 34 (23 - 178)	93 ± 54 (33 - 298)
GGT	72 ± 87 (14 - 727)	69 ± 57 (14 - 187)	98 ± 72 (35 - 277)	57 ± 43 (16 - 147)	74 ± 63 (16 - 287)	67 ± 112 (15 - 727)
Iron	20.3 ± 7.2 (5.6- 48.4)	21.0 ± 8.2 (7.7 - 31.2)	25.5 ± 8.5 (14.0 - 48.4)	20.6 ± 6.1 (11.5 - 29.6)	18.9 ± 6.4 (8.6 - 34.2)	19.5 ± 6.9 (5.6 - 35.5)
transf.-Saturat	27 ± 10.3 (7.8 - 67)	26.5 ± 10.9 (10 - 44.7)	35.6 ± 13.3 (13.8 - 67)	27.7 ± 9.6 (16.7 - 45.2)	24.9 ± 10 (9.1 - 48)	25.9 ± 8.8 (7.8 - 45)
a_2-macr globulin	3.3 ± 1 (1.2 - 5.7)	3.7 ± 1.2 (1.6 - 5.2)	3.9 ± 0.8 (2 - 4.9)	3.3 ± 0.7 (2.5 - 4.7)	3.2 ± 0.9 (1.2 - 5.1)	3 ± 1 (1.4 - 5.7)
IgG	13.6 ± 3.3 (7.8 - 23.2)	13.7 ± 3.1 (9.5 - 19.6)	15.3 ± 3.7 (9.3 - 21.4)	13.9 ± 3.8 (10.9 - 22.4)	13.7 ± 3.9 (8.6 - 23.2)	13 ± 2.5 (7.8 - 19.3)
IgA	2.04 ± 1.01 (0.47 - 4.57)	1.88 ± 0.92 (0.52 - 3.1)	2.5 ± 1.04 (1.32 - 4.33)	2.09 ± 0.97 (0.97 - 3.35)	1.81 ± 0.86 (0.47 - 3.47)	2.08 ± 1.09 (0.6 - 4.57)
AST/ALT	0.73 ± 0.26 (0.37 - 1.96)	0.65 ± 0.19 (0.43 - 1.06)	0.89 ± 0.31 (0.52 - 1.4)	0.72 ± 0.17 (0.48 - 0.96)	0.83 ± 0.33 (0.47 - 1.96)	0.66 ± 0.19 (0.37 - 1.22)
APRI	0.78 ± 0.64 (0.13 - 3.58)	0.77 ± 0.64 (0.33 - 2.52)	1.21 ± 0.96 (0.32 - 3.58)	0.7 ± 0.59 (0.27 - 2.03)	0.83 ± 0.7 (0.19 - 3.03)	0.66 ± 0.46 (0.13 - 2.3)
HALT-C	0.28 ± 0.2 (0.01 - 1)	0.26 ± 0.18 (0.04 - 0.56)	0.43 ± 0.3 (0.11 - 0.99)	0.31 ± 0.16 (0.14 - 0.59)	0.29 ± 0.21 (0.04 - 0.88)	0.24 ± 0.17 (0.01 - 1)
FORNS	4.67 ± 1.85 (-0.7 - 8.94)	5.39 ± 1.54 (3.36 - 7.83)	5.58 ± 1.68 (2.06 - 7.63)	4.83 ± 2.17 (2.32 - 8.63)	4.81 ± 1.74 (1.66 - 8.94)	4.14 ± 1.86 (-0.7 - 8.84)
FIB-4	1.8 ± 1.13 (0.26 - 5.38)	1.94 ± 1.21 (0.77 - 4.65)	2.38 ± 1.29 (0.63 - 5.38)	1.99 ± 1.51 (0.43 - 5.38)	1.84 ± 1.17 (0.45 - 5.16)	1.55 ± 0.95 (0.26 - 4.24)
HUI	0.10 ± 0.12 (0 - 0.55)	0.13 ± 0.1533 (0.02 - 0.46)	0.19 ± 0.17 (0.01 - 0.49)	0.1 ± 0.09 (0.01 - 0.25)	0.08 ± 0.09 (0.001 - 0.3)	0.08 ± 0.12 (0 - 0.55)
GUCI	0.89 ± 0.85 (0.14 - 4.87)	0.82 ± 0.70 (0.30 - 2.72)	1.41 ± 1.27 (0.35 - 4.87)	0.76 ± 0.68 (0.27 - 2.29)	0.91± 0.88 (0.19 – 4.00)	0.76 ± 0.71 (0.14- 3.98)
Fibro-Index	1.42 ± 0.59 (-0.54 - 2.8)	1.5 ± 0.66 (0.62 - 2.55)	1.74 ± 0.66 (0.67 - 2.8)	1.46 ± 0.34 (0.93 - 1.95)	1.4 ± 0.53 (0.23 - 2.76)	1.31 ± 0.61 (-0.54 - 2.75)
HEPA-SCORE	0.51 ± 0.31 (0.04 - 1)	0.61 ± 0.3 (0.17 - 0.96)	0.73 ± 0.3 (0.19 - 1)	0.53 ± 0.36 (0.15 - 1)	0.48 ± 0.27 (0.09 - 1)	0.44 ± 0.31 (0.04 - 1)
Fibro-Test	-0.03 ± 1.48 (-2.72 - 3.75)	0.73 ± 1.73 (-1.75 - 3.75)	0.88 ± 1.31 (-2.01 - 2.47)	-0.01 ± 1.30 (-2.23 - 1.62)	0.05 ± 1.32 (-1.88 - 3.34)	-0.51 ± 1.45 (-2.72 - 3.1)

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In CHB-patients, there was no such distinction, but the sample was too small (particularly considering the low viraemia responsiveness) to compare the response categories in this fashion.

SAFETY

Wellbeing and adverse events (AE)

There were 449 AE-records in 24/26 CHB-patients (92.3 %) and 1,887 AE-records (by visit) in 91/97 CHC-patients (93.8 %) over the course of the study. This corresponded with 206 AE-diagnoses (possibly extending over several visits) in CHB-patients, and 791 AE-diagnoses in CHC-patients.

Anaemia, leukopenia, thrombocytopenia, abdominal pain, nausea, vomiting, fatigue, feeling weak, fever, irritability, loss of appetite, muscle pain, headache, feeling depressed, and insomnia ranked as most frequent AE.

Most AEs were of mild intensity. In CHB-patients, of the 449 AE-records, no AE was reported of "severe" intensity, 428 were recorded as "mild" and 21 as "moderate". In the CHC-patients, of the 1,887 AE-records, 1,646 were labelled as "mild", 225 as "moderate", and 16 as "severe".

In 18 of the 26 enrolled CHB-patients and in 60 of the 98 enrolled CHC-patients who suffered at least one AE, medication was used to treat the AE (use of medication recorded in 83/449 AE-records and in 197/1887 AE-records for the CHB- and CHC-patients, respectively). This mostly related to headache, abdominal pain, liver pain, and fever. Most clinical AEs had resolved by the end of the study observation time; some of the laboratory test related AEs, although regressing, had not completely resolved by the end of the study.

Most AEs were recorded on-treatment and were reported as related to the medication used for treatment of chronic viral hepatitis. In CHB-patients, 58 of the 449 AE-records were considered unrelated to any study medication and 391 were considered related to the treatment of chronic hepatitis. No AEs were reported as related to NRL972 or to be due to an aggravation/progression of the primary diagnosis.

In CHC-patients, 197 of the 1887 AE-records were considered unrelated to treatment, 1674 were considered related to the treatment of chronic hepatitis and 2 to the aggravation/ progression of the primary diagnosis (including serious/severe anaemia in patient RO3-R009; hepatocellular carcinoma in patient RO3-R013). For CHC 14 AE-records in 4 CHC-patients were reported by the investigator to be at least possibly related to NRL972.

In one patient a life-threatening severe anaemia developed shortly after M03; the event required hospitalisation; the patient was discontinued from the trial prematurely. This SAE was reported to be due to an aggravation of the primary diagnosis; the earlier milder onset of the anaemia was reported to be related to the treatment of chronic viral hepatitis.

In one patient, very high levels of the tumour markers were identified at P06; upon further follow-up, the patient was diagnosed to have a hepatocellular carcinoma; while outside the observation window, the event was not reported as serious. The event was reported to be due to aggravation/progression of the primary diagnosis.

One further patient tested positive for pregnancy one month after visit P03; the patient was discontinued from the trial (reported as due to “other reasons”); the pregnancy was followed-up and was confirmed to have progressed to a term delivery without complications.

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Clinical laboratory tests

The treatment of chronic viral hepatitis was associated with changes in a number of laboratory tests described previously; in several patients, these changes led to Common Terminology Criteria for Adverse Events (CTCAE) Stage-III anomalies and several of the clinical laboratory-anomalies were reported as AEs.

All of these were considered related to treatment for chronic vital hepatitis, , except for 11 AEs in 4 CHC-patients that were reported to be at least possibly related to NRL972.

Physical examination

There were no relevant changes upon physical examination attributable to NRL972.

Vital functions

There were no relevant individual or average changes in blood pressure or pulse rate over the course of the study.

CONCLUSION

- Compared with healthy control subjects studied previously, patients with chronic viral hepatitis were found to have a slower NRL972-elimination on average (data at baseline, prior to treatment of chronic viral hepatitis): the mean ± SD (range) C(30):C(10)-ratio was 0.33 ± 0.13 (range: 0.16 to 0.66) and 0.41 (range: 0.19 to 0.80) in CHB- (N: 26) and CHC-patients (N: 89), respectively.
- The data were affected by substantial between-subject heterogeneity: some patients showed a particularly fast and some showed a particularly slow elimination of NRL972 and this heterogeneity was independent of baseline viraemia, various clinical laboratory tests and disease scores/indices; no correlation was found between the pharmacokinetics of NRL972 and any such (single) criterion.
- In contrast to other disease scores/indices, the pharmacokinetics of NRL972 indicated an average improvement in hepatobiliary transport function over the course of the treatment of chronic viral hepatitis C, which persisted after the treatment was terminated: the mean (± SD) C(30):C(10)-ratios by visit were 0.41 ± 0.13, 0.40 ± 0.13, 0.34 ± 0.12, and 0.33 ± 0.15 at baseline (N: 89), after six months of treatment (N: 85), after twelve months of treatment (N: 66), and six months after the end of treatment (N: 72), respectively.
- Based on the PCR viraemia data, the patients were assigned to various response categories (no-response; response, but not evaluable whether sustained; response which failed to be sustained; sustained response). Of the 98 enrolled CHC-patients, 77.6% achieved non-detectable viraemia on at least one on-treatment visit, albeit that the response was confirmed as not sustained in 25.5%. In most of the 26 enrolled CHB-patients, viraemia response was either not achieved (34.6%) or failed to be sustained (38.5%); with only 4 patients (15.4%) achieving sustained viraemia response.
- In general, the CHC non-responders tended to have a slower elimination of NRL972; at baseline, the mean (± SD) C(30):C(10)-ratio was 0.593 ± 0.169, 0.424 ± 0.115, and 0.349 ± 0.104 in viraemia non-responder (N: 8), viraemia responder who failed to sustain response (N:25), and viraemia responders with sustained response (N:41), respectively. This separation remained evident throughout the further course of the study i.e. during and after treatment of chronic viral hepatitis.
- CHC viraemia non-responders appear to be different from viraemia responders on several

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accounts. Although not exclusively, this distinction appeared to be particularly well expressed by NRL972-testing. • NRL972-testing was generally well tolerated. Only 14 AE-records in 4 CHC-patients were reported by the investigator to be at least possibly related to NRL972, and none for CHB. There was no indication of relevant individual or average changes in blood pressure or pulse rate over the course of the study.		
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