Norgine Ltd
Clinical Development
Norgine House, Widewater Place
Moorhall Road
Harefield, Uxbridge
Middlesex, UB9 6NS
United Kingdom (UK)
Tel: +44-(0)1895 826600
Fax: +44-(0)1895 825865

CLINICAL STUDY REPORT
CONFIDENTIAL

Study Title:	A multi-centre, open short term follow-up Phase II study to evaluate the clearance of NRL972 in patients undergoing alcohol withdrawal commencing in a controlled clinical setting
EudraCT No.:	2007-004663-22
Investigational Product:	NRL972 (fluorescein lisicol tri-sodium salt/ cholyl-L-lysine-fluorescein)
Indication:	Assessment of hepatic dysfunction in patients undergoing alcohol withdrawal
Study Design:	Multi-centre, open, single group study
Study Number:	NRL972-05/2007 (ETOH)
Development Phase:	II
Study Dates:	Date of first screening visit: 16 Jun 2008 Date of last follow-up visit: 21 Jan 2011
Coordinating Investigator:	[redacted], Zentralinstitut für Seelische [redacted], Germany
Sponsors Study Director:	[redacted], Norgine Ltd, Development, Norgine House, Widewater Place, Moorhall Road, Uxbridge UB9 6NS, UK
Signatures:	[redacted]
Date:	28 Nov 2011
GCP Compliance:	This study was conducted in accordance with Good Clinical Practice (GCP) guidelines, including the archiving of essential documents and local legislation.

2 SYNOPSIS

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

Title of the Study:
A multi-centre, open, short term follow-up Phase II study to evaluate the clearance of NRL972 in patients undergoing alcohol withdrawal commencing in a controlled clinical setting
Short title: NRL972 in patients attempting alcohol cessation

Coordinating Investigator:
[redacted]
Zentralinstitut für Seelische Gesundheit
[redacted]
Germany
[redacted]

Study Centre:
13 centres in Germany and Austria

Publication (Reference):
Not applicable

Studied Period:	**Phase of Development:**
16 Jun 2008 (date of first patient enrolled) 21 Jan 2011 (date of last patient completed)	Phase II

Objective:
To investigate the hepatic clearance of NRL972 in patients undergoing alcohol withdrawal therapy

Methodology:
Patients, aged between 18 to 75 years with a history of alcohol dependence, who were motivated to stop alcohol consumption, entered the study after written Informed Consent (IC) was obtained. Following the inclusion, the patients attended the clinic for assessment at Baseline and at the end of Week 2 and 4. At Baseline, Week 2 and Week 4, NRL972 was administered, and the patients were evaluated. Patients who were scheduled for further follow-up, might have received NRL972 at the end of the last week of withdrawal therapy (maximum: at the end of Week 6) if they were willing to

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

stay in the study for this length of time. The patients were followed for a stationary phase with subsequent ambulatory visits or attended for ambulatory visits only, dependent upon the standard clinical management approach at the individual study centres.

Number of Patients:

Planned:	Full Analysis Set (FAS): up to 180 patients
	Valid Cases Set (VCS): at least 100 patients
Actual:	Enrolled: 254 patients
	Safety Set (SAF): 198 patients
	FAS: 186 patients
	VCS: 141 patients

Diagnosis and Main Criteria for Inclusion:

All patients had to meet the following inclusion criteria:

- Patient has given his written IC to the study participation, prior to study-specific procedures
- Ethnicity: any
- Male and female (non-child-bearing potential, i.e. post-menopausal or medically adequate contraception)
- Age between 18 to 75 years
- Alcohol dependence according to Diagnostic and Statistical Manual of Mental Disorders, Ed. IV (DSM-IV-TR)
- A minimum of 2 years of alcohol dependence
- Last alcohol consumption within the last 28 days prior to inclusion in the study assured by successful detoxification (see below) and undergoing rehabilitation for alcohol withdrawal
- Successful completion of detoxification (no severe signs of withdrawal) and a minimum of 7 days of abstinence
- Motivation to stop alcohol consumption in a controlled clinical setting for at least 4 weeks
- Laboratory signs of alcohol-induced hepatic dysfunction, i.e. at least one Liver Function Test (LFT) >2x Upper Level of Normal (ULN)
- Medically fit to undergo the protocol-defined procedures without undue risk and discomfort

Test Product, Dose and Mode of Administration, Batch Number:

Substance:	Fluorescein lisicol tri-sodium salt
	Cholyl-L-lysine-fluorescein
	Cholyl-lysyl-fluorescein
Development code:	NRL972

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

Pharmaceutical form:	Solution for intravenous (iv) injection, 0.4 mg/mL solution, pre-filled syringes
Route of administration:	iv
Dosage:	Single application
Posology:	2 mg by 15-seconds iv-bolus injection
Batch Numbers:	NORp004, NORs003, NORt002 and NORx001

Duration of Treatment:
A total of up to 7 weeks per patient, i.e. up to 1 week of Screening and a maximum 6 weeks of Follow-Up (depending on the duration of the withdrawal therapy) were scheduled.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable

Criteria for Evaluation:

Primary Endpoint:
The primary investigational criterion was the clearance CL [mL/min] of NRL972 for the assessment of hepatic dysfunction in patients undergoing alcohol withdrawal.

Secondary Endpoints:
Secondary pharmacokinetic (PK) analysis using two-point fractional recovery concentrations and absolute C[60] concentration, comparing clearance (CL) and half-life ($t_{½}$) derived from the time course of the plasma concentration of NRL972 up to 60 minutes after injection and the two-point fractional recovery C[30]:C[10] concentration ratio and determination of standard PK variables. The analysis was conducted similarly as done for the primary endpoint.
Furthermore, clinical matrix parameters measuring impaired hepatic function were used to investigate the relationship to the PK of NRL972. The severity of hepatic dysfunction was documented using:

- Encephalopathy
- Disability/incapacity
- Subjective symptoms
- Objective symptoms
- Abdominal ultrasound
- Alcohol habits (Alcohol Use Disorder Identification Test [AUDIT] and validated structured interview F90)
- Clinical course
- Laboratory values (associated with hepatic disease conditions)

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

Safety Parameters:

- Type and frequency of adverse events
- Laboratory parameters (safety laboratory, including haematology, clinical chemistry, urinalysis)
- Clinical variables (vital signs and physical examination)
- Alcohol level

Statistical Methods:

Statistical Assumptions:

Primary objective: pre-post difference of the clearance (CL [mL/min]) of NRL972 after 4 weeks in comparison to the baseline assessment.

Secondary objective: investigation of secondary parameters (other PK variables and clinical severity matrix assessments) focussing on the correlation to the pre-post difference of the NRL972 clearance after 4 weeks and at the end of the withdrawal therapy (maximum: 6 weeks)

Sample size calculation:

A sample size of 100 was considered to have 80% power to detect an effect size of 0.283, using a paired t-test for the primary criterion with a 0.05 two-sided significance level. Assuming a standard deviation of 73 mL/min at each visit as determined in the previously conducted phase-II evaluation of patients with hepatic cirrhosis, the difference between the mean values calculated between the visits had to be at least 41.4 mL/min for this effect size. Based on the study design with at least a 4-week follow up (maximum: 6 weeks) and a patient population suffering from alcohol dependency, a maximum of 180 patients were considered necessary for the FAS with the aim of obtaining at least 100 patients for the VCS.

Pharmacokinetic analysis:

Using the t-test for paired samples for the primary parameter, the null hypothesis of no pre-post change in the clearance of NRL972 was tested two-sided on a significance level of 5%. If the normal assumption was essentially violated, the Wilcoxon signed-rank test was planned to be used instead.

All other parameters (including PK) were analysed descriptively with an exploratory intention.

The correlation of all other pre-post changes of the pharmacokinetic parameters was calculated.

Safety analysis:

Adverse events (AEs) were listed and a causality assessment was made in relation to the investigational medicinal product (IMP). Summary statistics were presented. Laboratory values were documented by the central laboratory with marking for alert ranges. Differences of the parameters were calculated with regard to baseline values; summary statistics including median values and

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

68% ranges were depicted.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Primary variable:

The present clinical phase II study was conducted to evaluate the association between hepatic dysfunction and the PK of NRL972 in patients with alcohol dependency and alcohol-induced impaired liver function undergoing alcohol withdrawal therapy.

The primary criterion of the study was the pre-post difference (baseline versus short term controlled alcohol withdrawal) of the clearance (CL [mL/min]) of NRL972. The baseline value at Day 1 was subtracted from the value after 4 weeks. Using the t-test for paired samples for the primary parameter, the null hypothesis of no pre-post change in the clearance of NRL972 was tested two-sided on a significance level of 5%.

For the patients in the VCS, the mean values of the clearance increased from 319.96 (± 195.891) mL/min at Visit V0 to 373.87 (± 228.959) mL/min at Visit V2 using the NRL972 concentration values measured at T10, T15, T30, T45 and T60. With regard to the pre-post difference, the null hypothesis was rejected when taking into account the NRL972 concentration values measured at T10, T15, T30, T45 and T60 ($p = 0.0018$) as well as for additional samples including the time points at T2, T5 and T7 ($p = 0.0034$).

In the subgroup analysis, there was a statistically significant difference ($p < 0.05$) for the subgroups of patients without cirrhosis, no relapse of alcohol abuse during the study and patients with cirrhosis and/or alcohol relapse or neither of the two. Furthermore, for the absence of continuous stable liver disease according to general medical history and no improvement of liver disease since its first diagnosis statistically significant differences were shown. In addition, statistically significant differences were shown for patients having no fibrosis and for patients with non-interpretable data according to the AST-to-platelet ratio index (APRI) score. These results were similar to that of the analyses including the data derived at the time points at T2, T5 and T7 (except for the subgroup of patients with cirrhosis and/or alcohol relapse).

A statistically significant increase in the clearance from Baseline to Visit V2/V3 was detected indicating an improvement of liver function. Therefore, the data suggest that the clearance of NRL972 from plasma may function as a measure of the functional capacity of the liver for the patients undergoing successful withdrawal therapy, including particularly patients without alcohol relapse during the study ($p = 0.0005$), worsened liver disease progression since its first diagnosis ($p = 0.0184$) or absence of fibrosis according to the APRI score ($p = 0.0095$).

In an analysis of potential influencing factors that may contribute to the large standard deviation (SD), a statistically significant link to C_{max} at Baseline was shown ($p = 0.0161$), indicating that the conduct of the NRL972 test may have a direct effect on the detected concentration values.

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

Secondary variables:

Differences between Baseline and the last available treatment visit for the alcohol withdrawal therapy:

One of the secondary objectives of the present study was to investigate the change in the clearance (CL [mL/min]) of NRL972 analogously to the primary analysis by subtracting the baseline value at Day 1 from the value at the end of the alcohol withdrawal therapy (maximum: 6 weeks).

Also for this pre-post difference, the null hypothesis was rejected for the analysis without the data derived at T2, T5 and T7 ($p = 0.0048$) as well as for including these data ($p = 0.0067$).

In the subgroup analysis, statistically significant differences ($p < 0.05$) were detected for the same subgroups as for the primary criterion.

In conclusion, an observation period of 6 weeks seems to be as suitable as the period of 4 weeks as analysed for the primary criterion.

Effect of liver status on the primary variable:

The effect of the liver status on the pre-post difference of the clearance values at Baseline and after 4 weeks but also for the last Follow-up Visit (including data up to Week 6) was analysed by using an analysis of variance (ANOVA) model.

Taking into account the NRL972 concentration values measured at T10, T15, T30, T45 and T60, no statistically significant effect of the liver disease progression since its first diagnosis on the pre-post difference V2/V3 - V0 of the clearance of NRL972 was shown ($p = 0.3307$). In addition, none of the three categories (unchanged, improved or worsened) showed a statistically significant effect ($p > 0.05$) in the analysis by using non-compartmental analysis (NCA). In the extended two-point analysis derived from C[30] and C[10], a significant effect was shown for improved versus worsened ($p = 0.0483$) but not for improved versus unchanged and not for unchanged versus worsened ($p > 0.05$) liver disease.

No statistically significant effect ($p > 0.05$) of the disease progression since the first diagnosis on the pre-post difference V2/V3 - V0 of the half-life of NRL972 was shown ($p = 0.4125$) as well as by one of the three categories (improved, worsened or unchanged) using NCA or the extended two-point analysis. Comparable results were obtained by an additional analysis including the data derived at T2, T5 and T7.

In addition, the impact of the liver status (improved, unchanged or worsened) at Baseline on the results of the primary variable was analysed. In the analysis by subgroup, taking into account the data derived at T10, T15, T30, T45 and T60, statistically significant differences ($p < 0.05$) in the change in clearance between Baseline and Visit V2/V3 were shown for the subgroup of patients with cirrhosis for improved versus unchanged liver disease progression and for improved versus worsened liver disease progression. Taking additionally into account the data derived at the time points T2, T5 and T7, statistically significant differences ($p < 0.05$) in the clearance were shown between the subgroup of patients with cirrhosis who showed an improved liver status at Baseline and the subgroup of patients

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

with cirrhosis who showed an unchanged or worsened liver status at Baseline.

In conclusion, patients who suffer from cirrhosis, which was unchanged or worsened before the start of the study, seem to be also a responsive cirrhosis target population for the NRL972 test. Overall, the NRL972 plasma elimination test is responsive to therapeutic interventions including patients with only minimal documented hepatic disease severity. It may provide a sensitive diagnostic tool to manage patients with liver conditions undergoing therapeutic interventions.

Concentration ratios:

Furthermore, the two-point fractional recovery C[30]:C[10], C[30]:C[15], C[45]:C[10], C[45]:C[15], C [60]:C[10] and C[60]:C[15] concentration ratios based on the observed values were analysed analogously to the primary variable.

As there was a statistically significant difference ($p < 0.05$) in the change of the concentration ratios between Baseline and Visit V2/V3, the null hypothesis was rejected for all concentration ratios except for C[45]:C[10] for the pre-post difference V3 - V0 and for C[60]:C[10] for the pre-post difference V3 - V0 as well as LV - V0 and for C[60]:C[15] for the pre-post difference V3 - V0.

In summary, the pre-post differences V2 - V0 and V2/V3 - V0 provide the clearest change for all concentration ratios. Especially for C[30]:C[15], C[45]:C[10] and C[45]:C[15], the changes are highly statistically significant ($p < 0.0001$). As the mean values of all pre-post differences are negative, an improved clearance over time was shown. The observed data are in-line with the results from the primary endpoint analysis using the clearance calculations (CL [mL/min]).

Clearance:

Estimates of the clearance were derived from the time course of the plasma concentrations of NRL972 up to 60 minutes after the injection for all visits. Estimates of the clearance were derived from the concentrations at all the originally designated time points (i.e. 10, 15, 30, 45 and 60 minutes) after the injection. Due to non-measurable concentrations at the dosing time, C[0] was set to C[10].

As there was a statistically significant difference ($p < 0.05$) in the change in clearance, the null hypothesis was rejected for all designated time points except the clearance derived from the designated time points T10 and T30 for the pre-post difference V1 - V0. Especially for the time point T15 and T60 for the pre-post difference LV - V0, a highly statistical significant change ($p < 0.0001$) was shown.

Apparent terminal disposition half-life ($t_{½}$):

By means of non-compartmental PK, estimates of the apparent terminal disposition half-life ($t_{½}$) were derived from the time course of the plasma concentrations of NRL972 up to 60 minutes after the injection for all visits (V0, V1, V2 and V3 [if applicable] and the last available treatment visit). Based on these estimates, the apparent terminal disposition half-life ($t_{½}$) was analysed analogously to the primary variable for all pre-post differences to the Baseline Visit V0.

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

As there was a statistically significant difference ($p < 0.05$) in the change of the apparent terminal disposition half-life, the null hypothesis, i.e. that there is no difference between the half-life values at the different designated time point, was rejected for the analysis of the half-life derived at the designated time point T10 and T30 for the pre-post difference V1 - V0. The null hypothesis was also rejected for the designated time point T15 and T30 for the pre-post differences V2 - V0 and V2/V3 - V0. The null hypothesis was also rejected for the designated time point T10 and T45 for the pre-post differences V1 - V0, V2 - V0 and V2/V3 - V0. The null hypothesis was also rejected for the designated time point T15 and T45 for the pre-post differences V1 - V0, V2 - V0, V2/V3 - V0 and LV - V0. The null hypothesis was also rejected for the designated time point T10 and T60 for the pre-post differences V1 - V0, V2 - V0 and V2/V3 - V0. The null hypothesis was also rejected for the designated time point T15 and T60 for the pre-post differences V1 - V0, V2 - V0 and V2/V3 - V0.

For the pre-post difference (V2/V3 - V0) of the terminal disposition half-life using the original time points by using NCA, a mean value of -2.39 (± 8.693) min was calculated. After the additional inclusion of the data derived at T2, T5 and T7, a similar pre-post difference of -2.42 (± 8.645) min was calculated. As the change of the terminal disposition half-life was negative, these data may be indicative of a recovery of the liver function during the alcohol withdrawal therapy.

Plasma concentration of NRL972 after 60 minutes C[60]:

The plasma concentration at 60 minutes after the injection C[60] was analysed analogously to the primary variable.

The mean plasma concentration of NRL972 measured at T60 decreased from 43.219 (± 47.2518) ng/mL at Visit V0 to 33.859 (± 44.0515) ng/mL at Visit V2.

For the pre-post difference between Baseline and Visit V2/V3, a mean value of -7.93 (± 28.158) mg/mL was calculated for the plasma concentration. As there was a statistically significant difference in the change in the plasma concentration ($p = 0.0014$), the null hypothesis was rejected.

A statistically significant difference ($p < 0.05$) for the change in the plasma concentration between Baseline and Visit V2/V3 was shown for the subgroup of patients with absence of cirrhosis, with no relapse of alcohol abuse, without cirrhosis and/or alcohol relapse. Furthermore, for patients with absence of continuous stable liver disease according to general medical history and no improvement of liver disease since its first diagnosis statistically significant differences were shown. In addition, there were statistically significant differences for patients with absence of fibrosis and with non-interpretable data according to the APRI score. Therefore, the null hypothesis, i.e. that there is no difference between the NRL972 concentration values at 60 minutes after the injection at Baseline and Visit V2/V3, was rejected for these changes.

The results indicate that the NRL972 test may function as a sensitive diagnostic tool, particularly in patients with alcoholic liver disease but without cirrhosis and/or alcohol relapse. Furthermore, there is evidence that the use of NRL972 as a diagnostic tool is most responsive in patients with stable liver disease since the diagnosis of chronic alcohol abuse. Furthermore, the target patients should have a history of an unchanged or worsened liver disease progression since its first diagnosis.

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

Other pharmacokinetic results:

The time course of the NRL972 concentrations in plasma was analysed non-compartmentally at all the originally designated time points T10, T15, T30, T45 and T60. Additionally, estimates of the clearance and the apparent terminal disposition half-life of cholyl-lysyl-fluorescein (CLF) were derived from the concentrations including those derived from the additionally designated time points (2, 5, 7, 10, 15, 30, 45 and 60 minutes) after the injection by means of NCA.

At Visit V0, a maximum concentration of 462.875 (± 103.9168) ng/mL was seen at the time point T2. A mean value for C_{max} of 285.08 (± 103.884) ng/mL was calculated compared to 373.61 (± 141.982) ng/mL including the data derived at T2, T5 and T7. The mean value for T_{max} was 10.1 (± 0.90) min compared to 6.6 (± 3.98) min including the more early data. With regard to CL, the mean value was 346.59 (± 213.210) mL/min compared to 298.79 (± 171.152) mL/min including T2, T5 and T7.

Taking into account the NRL972 concentration values measured at T10, T15, T30, T45 and T60, a mean pre-post difference for C_{max} of -14.87 (± 109.779) ng/mL and for CL of 45.54 (± 188.558) mL/min was calculated compared to a mean pre-post difference for Cmax of -4.73 (± 122.340) ng/mL and for CL of 33.43 (± 144.166) mL/min including the data at T2, T5 and T7.

With regard to the concentration ratios, the mean values for the pre-post differences varied between -0.0164 (± 0.09789) for C[60]:C[10] and 0.0370 (± 0.11454) for C[30]:C[15].

Additional analyses:

With regard to the hepatic disease scores that were analysed in this study, most of the patients were classified as mild stage of liver disease. At the Baseline Visit V0, 96.5% of the patients in the VCS were classified with Child-Turcotte-Pugh (CTP) class A and 3.5% with CTP class B. After the alcohol withdrawal period, nearly no change in the classification was seen. At the last available treatment visit, 97.2% of the patients were classified with CTP class A and 2.8% with CTP class B. As assessed by the other scores, nearly no change between Baseline and the last available treatment visit was detected. According to the prothrombin time, γ-GT, apolipoprotein A1 and α2-macroglobulin (PGAA) index, for approximately 90% of the patients in the VCS the presence of significant alcoholic liver disease/cirrhosis was unknown. The results of Göteborg University cirrhosis index (GUCI) even indicate that nearly 90% of the patients had no cirrhosis. Only for the hepatic dysfunction score (consisting of the parameters serum total bilirubin, prothrombin prolongation, serum lactate and encephalopathy grade), indicative of the hepatic disease severity, an improvement was shown. At Visit V0, 48.9% of the patients were classified as having no hepatic dysfunction compared with 63.1% at the last available treatment visit. A very low correlation between the change in the hepatic dysfunction score and the pre-post difference of the clearance (FAS: Spearman r = -0.1384, VCS: r = -0.1341) was determined.

The influence of the categorised hepatic dysfuntion score (none, mild, moderate or severe) on the clearance within an ANCOVA model was analysed by visit. Statistically significant influences were detected at Visits V0, V2, V3 and at the last attended visit after the first injection LV ($p < 0.05$) for the FAS. For the VCS, only at Visit V0 a significant influence of the hepatic dysfunction score on the

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

clearance was shown ($p < 0.05$).

In general, the hepatic scores as analysed in this study seem to be not sensitive enough to detect an improvement of the mild impaired liver function after an alcohol withdrawal therapy with a maximum of 6 weeks.

When comparing the laboratory parameters alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (γ-GT), lactate dehydrogenase (LDH), cholinesterase, total bilirubin, serum albumin, lactate, prothrombin time (PTT), ferritin and hyaluronic acid at Visit V-1 and end-of-trial (EOT), the median concentration values for nearly all parameters were within the reference ranges at both visits. For female patients, the ALT and AST values decreased from outside to inside the normal ranges during the study. With regard to γ-GT, the median values were outside the reference range for both gender on Baseline as well as on EOT but showed a considerable decrease towards the reference range. Therefore, the reference ranges of these parameters (which are assessed in many hepatic scores) are too broad to reflect the changes in the liver function during a withdrawal therapy of up to 6 weeks.

A statistically significant influence of alanine aminotransferase (ALP) on the pre-post difference of the clearance was shown ($p = 0.0211$). Besides, no influence of the other laboratory parameters was detected.

Nearly all of the laboratory parameters mentioned above showed a distinct response to the alcohol withdrawal therapy as shown by the pre-post differences between Visit V-1 and EOT indicative of liver regeneration.

In summary, the data generated during this study provide evidence that the NRL972 test may be used as a sensitive measure to analyse the liver function in patients undergoing an alcohol withdrawal therapy. For the patient subgroups and conditions as outlined above, the NRL972 test may represent a particular valuable diagnostic tool for monitoring the course of the liver function. Furthermore, NRL972 clearance is responsive to the observed hepatic improvements after short-term (4 to 6 weeks) therapeutic interventions.

SAFETY RESULTS:

No patient died during the course of the study. In the SAF (N = 198), 15 patients (7.6%) suffered from 16 treatment-emergent serious adverse events (SAEs) which were assessed as unrelated in 15 cases (93.8%) and as possibly related in 1 case (6.3%). Five patients (2.5%) of the SAF prematurely discontinued the study because of 5 treatment-emergent adverse events (TEAEs); 4 TEAEs (80.0%) thereof were assessed as unrelated and 1 TEAE (20.0%) as possibly related. The intensity of 4 of these TEAEs (80.0%) was moderate and of 1 TEAE (20.0%) severe.

The number of patients affected by any TEAE was 89 (44.9%). The number of episodes reported was 190, and the number of symptoms was 209. In the causality assessment to the administration of the IMP by the investigator, the majority of cases were assessed as unrelated (141 TEAEs [74.2%]) compared with 40 TEAEs (21.1%) assessed as possibly related and 9 TEAEs (4.7%) assessed as

Name of Sponsor/Company: Norgine Ltd	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Names of Active Ingredients: Cholyl-L-lysine-fluorescein; cholyl-lysyl-fluorescein; fluorescein lisicol tri-sodium salt		

probably related.

The intensity of the TEAEs was reported as mild in 119 cases (62.6%), as moderate in 63 cases (33.2%) and as severe in 8 cases (4.2%).

The most prominent System Organ Classes (SOCs) with regard to the patients with the respective TEAE symptoms were psychiatric disorders (27 patients [13.6%] were affected by 32 TEAE symptoms), general disorders and administration site conditions (18 patients [9.1%] were affected by 24 TEAE symptoms), gastrointestinal (GI) disorders (18 patients [9.1%] were affected by 22 TEAE symptoms) and infections and infestations (18 patients [9.1%] were affected by 21 TEAE symptoms).

The most frequently recorded TEAE symptoms by PT were nasopharyngitis (13 patients [6.6%] were affected by 13 symptoms), alcoholism (11 patients [5.6%] were affected by 12 symptoms) and condition aggravated (10 patients [5.1%] were affected by 10 symptoms, documenting the relapse of alcohol abuse as a TEAE.

Taken together, the reported adverse event (AE) profile within this study was in accordance with the safety profile of NRL972 as shown in the previously conducted studies, including also different patient populations with hepatic cirrhosis and all degrees of liver impairment.

With regard to the laboratory parameters assessed, all 198 patients (100.0%) had at least one value outside the normal range limits at the Baseline/Screening Visit as well as all 179 patients (90.4%) with available data at the EOT Visit/last available treatment visit. With regard to the pre-post differences between the EOT and the Screening Visit V-1, only minor changes were recorded. In the vital signs, none of the parameters assessed showed systematically or relevant changes during the course of the study.

In conclusion, the administration of NRL972 proved to be generally well tolerated in a population of patients undergoing alcohol withdrawal. Furthermore, the safety data are in-line with the so far known safety profile of NRL972 in patients with various forms of hepatic disease.

CONCLUSION:

In summary, the results of the present study corroborated the role of NRL972 as a potential sensitive measure in the monitoring of alcohol-induced hepatic dysfunction/impairment, especially in patients with no relapse of alcohol abuse and milder forms of hepatic disease (i.e. without cirrhosis and significant fibrosis).

Date of the Report:
28 Nov 2011