Title of the Study:
An open, randomised study to compare the reproducibility of CTP rating and NRL972 pharmacokinetics in patient volunteers with hepatic cirrhosis

Short Title:
Reproducibility of CTP staging and NRL972 PK in hepatic cirrhosis

Principal Investigator:
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Coordinating Study Centre:
Timisoara, Romania

Study Centres:
Enrolment of patient volunteers with hepatic cirrhosis was managed by the co-ordinating phase I centre. Subsequent visits for the randomised rater assessment were then arranged at the co-ordinating centre for patient volunteers to undergo evaluation by one of the rater pairs. Each rater pair was formed of two qualified physicians with the knowledge and expertise to perform the necessary assessments related to the clinical evaluation of cirrhotic patient volunteers. Each rater was assigned with his accredited clinical laboratory for the assessment of the required blood parameters.

Publication (Reference):
Not applicable

Studied Period:	**Phase of Development:**
27 Apr 2009 (date of first patient volunteer enrolled) 12 Jan 2010 (date of last patient volunteer completed)	Phase I

Objectives:
The objective of the current study was to compare the reliability of the Child-Turcotte-Pugh (CTP) sum score and the NRL972 ratio with the general goal to show that, under consideration of relevant factors which influence the reproducibility, the rating based on the CTP sum score is less reproducible than the rating based on the pharmacokinetics of NRL972 (based on the C[30]:C[10] concentration ratio) in patient volunteers with clinically confirmed stable hepatic cirrhosis.

Methodology:
This was an open randomised study, using a phase I unit as a single-centre to coordinate the study conduct allowing a comparison of the reproducibility of CTP versus NRL972 pharmacokinetics in patient volunteers with hepatic cirrhosis of different severities. In the primary analysis, a categorical variable (CTP score value) was compared for its reproducibility against a continuous variable (NRL972 clearance using the C[30]:C[10] concentration ratio). The overall study results need to be considered for its reproducibility of both parameters in clinical settings of cirrhosis.

Number of Patient Volunteers:

Planned: Number of rater pairs: 32 to 40
Number of patient volunteers: 6 eligible patient volunteers with clinically established hepatic cirrhosis per rater pair
To be recruited: 240 patient volunteers with hepatic cirrhosis to ensure that 192 completed the study

Actual: Number of rater pairs: 33
Screened: 195 patients
Safety Set (SAF): 195 patients
Full Analysis Set (FAS): 195 patients
Valid Cases Set (VCS): 170 patients

Diagnosis and Main Criteria for Inclusion:

All patient volunteers with clinically confirmed hepatic cirrhosis who were included in the study had to meet the following inclusion criteria:

- Able to give written Informed Consent
- Gender: male and female (non-childbearing potential, i.e. post-menopausal or medically adequate contraception)
- Ethnicity: any
- Age: 18 to 80 years of age
- Patient volunteers with a diagnosis of clinically stable hepatic cirrhosis with a CTP class A, B or C but excluding patient volunteers with the diagnosis of primary biliary cirrhosis, primary sclerosing cholangitis and cystic fibrosis-associated liver disease
- No previous liver transplantation or intended liver transplantation within the next 6 months after enrolment
- No previous transjugular intrahepatic portosystemic shunt (TIPS) or portocaval anastomosis (PCA)
- Medically fit to undergo the protocol-defined procedures without undue risk and discomfort
- No previous participation in a study with an investigational product within 90 days prior to enrolment except epidemiologic or observational studies

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

Substance:	Cholyl-L-lysine-fluorescein Cholyl-lysyl-fluorescein Fluorescein lisicol tri-sodium salt
Development code:	NRL972
Pharmaceutical form:	Solution for injection (0.4 mg/mL)
Route of administration:	iv-injection
Strength:	2 mg/5 mL
Posology:	15-second iv injection of 2 mg in 5 mL
Batch number:	NORt002 (expiration date 19 Nov 2010)

Course of the Study:
The rating was performed by 33 pairs of raters. The raters performed the required assessments in their capacity of sub-investigators of the phase I (coordinating) unit. Patient volunteers with clinically stable hepatic cirrhosis of either CTP class A, B or C, aged between 18 and 80 years entered the study after written Informed Consent was obtained. After inclusion, the rating based on the CTP sum scores and pharmacokinetics of NRL972 was assessed by a rater pair in a randomised design. After the screening, the patient volunteers were randomised to a rating sequence as follows: Visit V1 rating was performed by the coordinating centre; Visit V2 and V3 ratings were performed by a pair of raters, each rater performed one visit. The final rating at Visit V4 was a second assessment by one of the previous raters by a random selection in accordance with the randomisation schedule.

Duration of Treatment/Observation per Patient Volunteer:
Evaluation of the investigational parameters was conducted at four different time points during a period of up to 6 weeks.

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

Investigational Parameters:
- The difference between the two ratings, comparing C[30]:C[10], apparent terminal disposition half life ($t_{½}$) and clearance (CL) for NRL972 (continuous variables) to the CTP sum score (categorical variable)
- The reproducibility of the CTP and NRL972 ratings, i.e. the difference between the two ratings given by one rater pair

Tolerability:
- Well-being and adverse events (AEs) (throughout the study)
- Clinical laboratory tests at screening following the administration of NRL972
- Vital functions (systolic blood pressure [SBP], diastolic blood pressure [DBP] and pulse rate [PR]): at the Screening Visit, prior to and 1 hour after the NRL972 injection

Statistical Methods:
Primary Objective:
To compare the reproducibility of the CTP sum score to the pharmacokinetics of NRL972 (based on the C[30]:C[10] concentration ratio) under consideration of relevant factors which influence the reproducibility. Both assessments were performed by a rater pair in patient volunteers with clinically confirmed stable hepatic cirrhosis.
The dependent variable within a linear-mixed model was the absolute difference between two ratings given by one rater pair, measured as percentage in relation to the mean of both ratings.
The test itself and the random effect of each rater pair, along with the random effect of the individual patient volunteer, had to be taken into account as influencing factors.
The contrast of the test effect (CTP-NRL972) was estimated if the 95% confidence interval lay completely above 0; in that case, superiority of NRL972 could be concluded.

Secondary Objectives:

- Within the model, the rater effect was investigated based upon the point estimation and the respective 95% confidence interval
- In an additional model, the CTP class (A, B or C) was taken into account. Contrasts and least square means were determined
- Analyses for inter- and intra-reproducibility of NRL972 values were performed
- The reproducibility, safety and tolerability of the four doses of 2 mg NRL972 by iv-injection in patient volunteers with different stages of hepatic cirrhosis was described

Sample Size Calculation:

A sample size of 64 rater pairs was considered to have 80% power to detect a difference in means of 10, assuming that the common standard deviation (SD) is 20 using a two-group t-test with an α of 5% two-sided significance level. For each rater pair, one of the ratings was combined with the rating of the respective coordinating centre to form an additional rater pair to reduce the number of rater pairs required to 32 to 40.

SUMMARY – CONCLUSIONS

RESULTS OF THE RELIABILITY OF LIVER CIRRHOSIS SEVERITY ASSESSMENT USING CTP AND NRL972 PHARMACOKINETIC ANALYSES:

The aim of this study was to evaluate the usefulness of NRL972 for liver cirrhosis severity assessment and staging while the main focus resided on comparing the reliability of the CTP sum score (categorical variable with values between 5 and 15 points) with the ratio of the serum concentration of NRL972 after 30 minutes and 10 minutes, C[30]:C[10] (continuous variable with values between 0 and 1).

For the primary analysis, the reliability was assessed by a conservative comparison using the difference between the ratings of a rater pair which were normed regarding the mean of the two ratings for that respective pair and was analysed within a mixed linear model. The result of this primary analysis was that over all patient volunteers, no difference in the reliability of the two test methods (CTP sum score and NRL972 ratio) could be shown. Furthermore, for the additional subgroup analysis based on the CTP class at the beginning of the study, a more detailed pattern was emerging. For the patient volunteers with CTP class A, the CTP score was significantly more reliable than the NRL972 ratio ($p = 0.0002$), while for the patient volunteers with CTP classes B and C the NRL972 ratio was more reliable than the CTP score ($p < 0.0001$ and $p = 0.0014$, respectively). It is remarkable that a patient with a CTP sum score of 5 or 6 (values for CTP A classification) has a normal clinical presentation or only minimal pathological alterations, while the NRL972 clearance values for CTP class A patients indicate clearly abnormal liver function.

In order to analyse the potential influence of the clinical stability of cirrhosis patients with regard to the CTP classification, the patient-wise coefficient of variation (CV) was calculated by using the four values from Visit V1 to V4. Only patient volunteers with useable values at all four visits were considered. A patient volunteer was defined as clinically stable if the CTP classification was unchanged at all four visits.

First of all, the percentage of clinically stable patient volunteers with hepatic cirrhosis differed considerably between the different CTP classes. A total of 69.6% of the patient volunteers with a CTP class of A at Visit V0 were stable over the four visits while for the other groups this percentage was 13.0% (CTP class B) and 42.1% (CTP class C). The patient-wise CV revealed that if the patient volunteer was not stable based on the CTP class over the four visits, the CV for the CTP score was much higher than if they would have been classified as stable. This was to be expected, as the CTP class was involved in the definition of clinical stability. However, for the NRL972 test the CV did not differ depending on the status of stability within the subgroups. This led to the assumption that the different distributions of stable patient volunteers within the three subgroups could have influenced the results of the primary analysis.

Therefore, the stability between two measurements was taken into account as another factor in the mixed model. Overall and in all CTP subgroups, the reliability estimator of the NRL972 ratio showed a

better value than the CTP score, and with the exception of patient volunteers with an initial CTP class of A, this difference was highly significant with $p < 0.0001$. Thus, it was possible to successfully determine an additional critical factor that had an influence on the results of the primary analysis. Taking this factor into account, the results were favourable for the NRL972 ratio with a better reliability as severity assessment tool.

Considering other influences did not reveal further factors. Neither the random rater effect nor the effect of the duration between measurements had a significant influence on the reliability. Integrating both effects into the same model, the rater effect became significant for the overall patient population ($p = 0.0148$). This could be explained by the fact that not many differences in the time window between measurements existed as most raters kept the planned seven-day schedule. The linear model will correct the estimators depending on the durations; it also has to correct the estimators for rater effects for all raters who had other durations. As the number of these raters was low, this could have caused a rater effect when looking simultaneously at the duration.

Concomitant medications did not reveal any notable influence. For the FAS, only the intake of Silimarina yielded a significant difference ($p = 0.0139$) in patient volunteers with CTP class B. In the VCS, a significant effect on the reliability was only shown for beta blockers for patient volunteers with CTP class A ($p = 0.0134$) and for diuretics for CTP class B ($p = 0.0317$). For both populations, 3 out of 40 tests showed a significant result. With a significance level of 5%, 5% of the tests were expected to show a significant result even in the absence of any influence. The slightly higher percentage of significant tests found did not give any reason for concerns of concomitant medication effects on the reliability.

In all models with additional influence factors, the estimators for the reliability of the CTP score and the NRL972 ratio did not change in a way which turned significance into non-significance or vice versa.

The only additional influencing factor showing a difference was the CTP class. When the CTP class and the interaction between the CTP class and test (CTP sum score or NRL972 ratio) were added to the mixed model, the interaction had a significant influence on the reliability ($p < 0.0001$). The estimators in the overall patient group then showed that the NRL972 ratio was significantly more reliable than the CTP score ($p = 0.0004$). These results reconfirmed the findings of the stability analysis using the CTP class. The stability of patient volunteers was different in the different CTP classes and had an influence on the results. Therefore, it seems that the interaction between the CTP class and test should give a result in the same direction as the stability analysis.

In order to investigate the reason for these differences, a three-way random effects model was applied to the parameters NRL972 ratio, albumin, alanine aminotransferase (ALT), asparate transaminase (AST), bilirubin and the International Normalised Ratio (INR) to assess the percentage of the variance explained by the effect of patient volunteers (disease severity), raters and visits compared to the total variance. The results showed for the NRL972 ratio that most of the variance was due to patient factors (e.g. the effect of different disease severities of the included patient volunteers) while the effect of having different raters only accounted for up to 7.4% (CTP class C) of the observed variance. For the laboratory parameters used in the calculation of the CTP score, the percentage of variance explained by the rater was much higher based on the laboratory results. The most notable parameter was the INR. Here, in all three subgroups more of the variance was explained by the raters (laboratory variance) than by the patient volunteers (disease severity). For example, in patient volunteers with CTP class A at the beginning of the study more than half of the variance in INR was due to the raters (57.6%), while only 20.5% of the variance could be explained by the difference in patient volunteers. The degree of the laboratory variance indicates that even some of the measured laboratory parameters used to calculate the CTP sum score are highly variable.

In addition, the reliability between raters and for the same rater was evaluated by assessing the inter- and intra-rater reliability using the Intraclass Correlation Coefficient (ICC). When comparing the raters at Visit V2 and V3, the NRL972 ratio achieved a high inter-rater-reliability of 0.868, while the CTP score achieved 0.755. In all CTP class subgroups, the NRL972 ratio demonstrated a higher reliability than the CTP score, but the absolute values were lower than in the overall group. On one hand, a possible explanation may be the lower number of patient volunteers grouped into the advanced cirrhosis

stages, particularly the CTP class C. On the other hand, it is easier to separate a whole patient collective with a different extent of severity than patient volunteers of comparable severity with narrow margins. The acceptable reliability for the CTP score for all patient volunteers with hepatic cirrhosis in contrast to the low reliability in the CTP class subgroups (less than 0.5) indicates that the CTP score might be able to give an idea of the severity of the liver disease but does not allow dividing individual patient volunteers into subtle degrees of disease severities. In this regard, the NRL972 ratio gave a better result, but a decreased reliability was observed in the CTP classes B and C, which is either related to higher variance in patient volunteers with a higher grade of cirrhosis severity, incorrect classification by the CTP class or the lower overall number of advanced cases in the study. CTP class B patients represent a mixed population with cases of either more mild disease, up to advanced cirrhosis conditions.

The difference in the ratings was also assessed by calculating the limits of agreement. Here, the repeatability index was of particular interest. It provides an estimate on the distribution of the difference around the general shift between the two raters. As the general shift was nearly zero for most of the parameters examined, it could be assumed that 95% of patient volunteers had an absolute difference between the two ratings that was less than the repeatability index. The repeatability index for all patient volunteers and for the raters at Visit V2 and V3 was 0.1880 for the NRL972 ratio. As this measure ranged from 0 and 1, this constituted 18.8% of that range. The respective repeatability index for the CTP score was 2.74 points. As this score has a range from 5 to 15, the repeatability index constituted 27.4% of that range, which is another result in favour of the NRL972 ratio. In addition to the numeric comparison, it seems to be worthwhile to compare this result to the clinical value of the classification used. Patients with 5 or 6 points counted as CTP class A without relevant clinical and laboratory findings within the CTP score (mainly normal ranges). On the other side, the presence of moderate abnormalities counts for 7 to 9 points and a CTP class of B, or the presence of severe clinical signs of cirrhosis counts for 10 or more points and a CTP class of C. If the class boundaries have a difference of 2 or 3 points from each other, a repeatability index of 2.74 points is clearly not clinically adequate to ensure a good severity assessment of the present hepatic cirrhosis.

Regarding the laboratory parameters as used in the calculation of the CTP score, the prothrombin prolongation showed a repeatability index of 6.87 seconds (s) for the overall cirrhosis population. With times of 0 to 4 s, 4 to 6 s and 6 s or more, this is no acceptable spread and reconfirms the results seen for the INR within the assessment of the different variance components. For the other two parameters, the repeatability index was also higher than the spread of the middle class of scoring, but not that drastic as for the prothrombin prolongation (24.91 µmol/L for bilirubin with a middle class range of 34.2-51.3 µmol/L and 9.92 g/L for albumin with a middle class range of 28-35 g/L).

When assessing the intra-rater reliability between the rater at Visit V4 and his previous measurement at either Visit V2 or V3, the reliability increased while the corresponding repeatability indices decreased accordingly. This was to be expected since the variance caused by different raters was no longer present. The NRL972 ratio had an acceptable intra-rater reliability of over 0.7 in the overall patient group with hepatic cirrhosis but also all subgroups and was higher than the observed reliability for the CTP score. For the repeatability index, the results were similar as to the inter-rater reliability with a repeatability index for the NRL972 ratio of 0.1685 and 2.16 points for the CTP score. For the laboratory parameters as used for the CTP score, the repeatability index was similar with 19.9 µmol/L for bilirubin, 9.09 g/L for albumin and 4.03 s for prothrombin prolongation.

As each NRL972 sample was split into four aliquots, both laboratories analysed two samples each, allowing an inter- and intra-laboratory reproducibility assessment for NRL972 values. Nearly all these comparisons of the reliabilities showed an acceptable result of over 0.9 in the overall patient group and a repeatability index between 0.1081 and 0.1392.

It is important to have reliable and reproducible data, but this is only clinically relevant if the variance in the data is clinically meaningful. The pharamacokinetic analysis of the NRL972 samples showed a clear link of the NRL972 test to the severity of the present hepatic cirrhosis. The C[30]:C[10] ratio was abnormal and elevated in the overall patient volunteer population. The lowest values were observed in patient volunteers classified as CTP class A (mean: 0.5073) compared to patient volunteers of CTP

class B (mean: 0.7226) and patient volunteers of CTP class C (mean: 0.7818). These results reconfirm that it might be more difficult to distinguish between patients classified as either CTP class B or C. It needs to be noticed that the CTP classification is a categorical rating and may not provide enough separation in the more advanced disease stages. The group-wise mean values for the other NRL972 pharmacokinetic parameters could also be linked to the cirrhosis severity, e.g. the half-life mean value increased with increasing severity (from 28.97 min in CTP class A over 60.10 min in CTP class B to 89.47 min in CTP class C) while the clearance decreased (from 157.97 mL/min in CTP class A over 70.63 mL/min in CTP class B to 51.19 mL/min in CTP class C). Thus, the pharmacokinetic properties of NRL972 allow conclusions to be drawn on the disease severity of patients with hepatic cirrhosis.

These pharmacokinetic results can, however, be slightly modified when including more early time points. For a subset of patient volunteers, additional blood samples were obtained during Visit V1 (Coordinating Rater [CR]: phase I unit) at two and seven minutes after the injection. When comparing the two pharmacokinetic profiles (i.e. with and without the additional early pharmacokinetic data), several differences were found. The time of the maximum concentration shifted from 5 minutes to 2 minutes for most patient volunteers, meaning that with the original timing of sampling the time point of the maximum concentration would have most likely been missed. As a consequence, the maximum concentration was also higher when integrating the additional measurements. This had a direct impact on the half-life and clearance, which decreased, and on the different areas under the curves (AUCs), which increased. However, these changes were relatively low in their absolute values.

Finally, several results of the CIR study (NRL972-03/2006) were repeated in the present study. A cut-off value of 0.313 has been previously identified for the NRL972 C[30]:C[10] ratio to be robust to separate healthy volunteers from patients with cirrhosis. Furthermore, all patient volunteers in this study were diagnosed with cirrhosis, which allowed the assessment of the sensitivity of this cut-off to detect cirrhosis. This analysis revealed that for 89.2% to 90.7% of the patient volunteers (depending on the visit) the NRL972 ratio was above the cut-off. Additionally, for less than 7.3% of the patient volunteers the NRL972 ratio crossed this cut-off in one of the possible directions. This means that the NRL972 ratio had a sensitivity of about 90% for detecting cirrhosis when using the stated cut-off and showed a low fluctuation in the results obtained. The same analysis for the other hepatic scores examined in this study delivered the best results for the prothrombin time, γ-glutamyltransferase, apolipoprotein A1, α2-macroglobulin (PGAA) score with a maximal sensitivity of 81.5%. The score with the lowest fluctuation was the non-alcoholic fatty liver disease (NAFLD) fibrosis score with only 6.9% observed switches. This means that the NRL972 ratio was more reliable than all other hepatic scores analysed when it comes to the non-invasive detection of liver cirrhosis while also having a low rate of diagnosis switches.

Additionally, patient volunteers were categorised into normal and abnormal liver function using the NRL972 ratio cut-off of 0.313. Subsequently, the sensitivity and specificity of the other hepatic scores were calculated. Interestingly, the positive predictive value for all other scores was high (at least 94%), while the negative predictive value for all the other scores was low (below 58.3%). This suggests that the other scores are not as sensitive as the NRL972 ratio. If a patient volunteer was rated to have an abnormal liver function by a score, most of them also had it based on the NRL972 ratio. Interestingly, in the cases rated as absence of cirrhosis by the other scores, there were a relevant number of patient volunteers with an abnormal liver function according to the NRL972 ratio. This indicates that most of the established hepatic scores are able to detect severe cases of hepatic cirrhosis but could miss a significant number of cases with an early stage of cirrhosis.

The NRL972-03/2006 (CIR) study determined cut-offs for mapping NRL972 pharmacokinetic results into the three CTP classes. These cut-offs were re-evaluated in the present study. For the majority of the patient volunteers classified as CTP classes A and C, the use of the four parameters C[30]:C[10], half-life, clearance and C[60] mostly confirmed the original CTP classification. However, if patient volunteers with clinically established cirrhosis were classified as CTP class B by the NRL972 parameters, this was only linked to the original CTP class in less than 50% of them. Further studies need to confirm which classification provides a better characterisation of the severity of cirrhosis in individual patients.

This result was also found when calculating the sensitivity and specificity of the cut-offs against the true CTP class. For the cut-off between the CTP classes A and B, the sensitivity ranged from 59.4% to 80.7% and the specificity from 65.2% to 80.3%. For the cut-off between CTP classes B and C, the sensitivity ranged from 56.8% to 65.9% while the specificity was between 68.3% and 70.8%. This indicates that both the CTP class and the pharmacokinetic parameters based on NRL972 can be used to measure the disease severity of patients with hepatic cirrhosis. A direct translation of the NRL972 results into the corresponding CTP classes is not always possible and may oversimplify the biological value assessed with both test systems.
The frequencies of class changes between Visits V1 and V4 by NRL972 parameters and CTP class were analysed as well. The results showed that none of the NRL972 parameters revealed more class changes between different visits than the original CTP class. In contrast, for the parameters C[60] and clearance the number of class changes was significantly lower than for the original class definition ($p = 0.0010$ and 0.0001, respectively). A classification using NRL972 parameters seems to be more stable.
This result was reconfirmed when calculating kappa-statistics between the ratings of different raters and the same raters. Here, the classification done by the NRL972 ratio did always result in a higher kappa than the CTP class. However, the differences were not statistically significant.
During study NRL972-03/2006 (CIR), six classes of NRL972 concentration ratios were defined (termed N1 to N6). In this study (NRL972-11/2008 (PAIR)), the patient volunteers of CTP class A were mainly assigned to class N1, whereas the classification of the patient volunteers of CTP classes B and C showed a clear shift towards higher classes.
In summary, the study results show that NRL972 is a useful tool for severity assessment and staging of patients with liver cirrhosis. The pharmacokinetic properties of NRL972 are able to show the impaired functionality of the liver with a dependency on the degree of hepatic damage in patients with cirrhosis. Nearly all evaluations allow the interpretation that the NRL972 test has a higher degree of reliability and repeatability than the test based on the CTP sum score. In addition, the results also suggest that the NRL972 ratio is a more sensitive tool to detect cirrhosis when compared to other established non-invasive hepatic scores for the assessment of cirrhosis.

SAFETY RESULTS:
No patient volunteer died during the course of the study. In the SAF, 4 patient volunteers (2.1%) suffered from 4 treatment-emergent serious AEs (SAEs) (1 patient volunteer (2.1%) with CTP class B and 3 patient volunteers (15.0%) with CTP class C). All SAEs were assessed as unrelated to the administration of the Investigational Medicinal Product (IMP). Two patient volunteers (1.0%) with CTP class C prematurely withdrew from the study due to 2 treatment-emergent AE (TEAE) symptoms which were assessed as unrelated by the investigator (1 of moderate and 1 of severe intensity).
TEAEs were reported for patient volunteers in all hepatic cirrhosis CTP classes. The number of patient volunteers affected by any TEAE was 50 (25.6%) (CTP class A: 28 (patient volunteers (21.9%), CTP class B: 13 patient volunteers (27.7%), CTP class C: 9 (patient volunteers (45.0%)). The number of episodes reported was 66 as well as the number of symptoms.
In the causality assessment to the administration of the IMP by the investigator, the majority of cases were assessed as unrelated (60 TEAEs (90.9%), CTP class A: 32 TEAEs (91.4%), CTP class B: 14 TEAEs (82.4%), CTP class C: 14 TEAEs (100.0%)), 6 TEAEs (9.1%) as possibly related (CTP class A: 3 TEAEs (8.6%), CTP class B: 3 TEAEs (17.6%), CTP class C: 0 TEAEs (0.0%)) and no TEAE as probably related.
The intensity of the TEAE symptoms was reported as mild in 23 cases (34.8%) (CTP class A: 16 cases (45.7%), CTP class B: 5 cases (29.4%), CTP class C: 2 cases (14.3%)), moderate in 39 cases (59.1%) (CTP class A: 18 cases (51.4%), CTP class B: 12 cases (70.6%), CTP class C: 9 cases (64.3%)) and severe in 4 cases (6.1%) (CTP class A: 1 case (2.9%), CTP class B: 0 cases (0.0%), CTP class C: 3 cases (21.4%)).
The most prominent System Organ Classes (SOCs) with regard to the cirrhosis patients with the respective symptoms were gastrointestinal disorders (5 patient volunteers (3.9%) with CTP class A

were affected by 6 TEAE symptoms, 5 patient volunteers (10.6%) with CTP class B were affected by 6 TEAE symptoms and 4 patient volunteers (20.0%) with CTP class C were affected by 7 TEAE symptoms) and nervous system disorders (7 patient volunteers (5.5%) with CTP class A were affected by 8 TEAE symptoms, 2 patient volunteers (4.3%) with CTP class B were affected by 2 TEAE symptoms and 3 patient volunteers (15.0%) with CTP class C were affected by 3 TEAE symptoms). The most frequently recorded TEAE symptom by Preferred Term (PT) was headache (CTP class A: 5 patient volunteers (3.9%) were affected by 6 TEAE symptoms, CTP class B: 1 patient volunteer (2.1%) was affected by 1 TEAE symptom, CTP class C: 3 patient volunteers (15.0%) were affected by 3 TEAE symptoms).

Combined, the reported AE profile within this study was in accordance with the safety profile of NRL972 as shown in the previously conducted studies.
All 195 patient volunteers (100.0%) in the SAF had at least one laboratory value outside the normal range limits at the Screening Visit V0 as well as at the End-of-Study Visit. With regard to the pre-post differences of the safety laboratory parameters between the End-of-Study and the Screening Visit V0, only minor changes were recorded. In the vital signs, none of the parameters assessed showed systematic or relevant changes during the course of the study.
In conclusion, the administration of NRL972 proved to be generally well tolerated, and the safety data are in-line with the so far known safety profile which is consistent also in the medically compromised hepatic cirrhosis population.

CONCLUSION:
In summary, the results of the present study outlined the high potential of the NRL972 test as a reliable measure to screen for the presence of hepatic cirrhosis, but also to assess in a reproducible manner, the severity and stage of cirrhosis.

Norgine discontinued the development of NRL972 in July 2013.