Synopsis – Study 15871A

Study Title

Exploratory, interventional, open-label, fixed-dose study with Selincro® as-needed use, in alcohol dependent patients with liver impairment

Investigators

[redacted]

(designated the *signatory investigator* for this study)

[redacted]

Study Sites

Medizinische Klinik, Krankenhaus Salem und Alkoholforschungszentrum, Heidelberg, Germany

Zentralinstitut für Seelische Gesundheit, Mannheim, Germany

Publications

None (as of the date of this report)

Study Period

First patient first visit – 17 September 2014 (the date when the first *Informed Consent Form* was signed)

Last patient last visit – 3 December 2015 (the date of the last protocol-specified contact with any patient)

Objectives

- *Exploratory objectives*:
  - to explore the reduction of alcohol consumption
  - to explore the change in liver stiffness
  - to explore the change in controlled attenuation parameter (CAP)
  - to explore the change in liver enzymes
  - to explore the shift in fibrosis stage
  - to explore the association between reduction of alcohol consumption, liver stiffness, CAP, and liver enzymes
  - to explore the change in Clinical Global Impression
  - to explore the change in quality of life
- *Safety objective*:
  - to evaluate the safety and tolerability of nalmefene

Study Methodology

- This was an interventional, prospective, national, two-site, open-label, fixed-dose study.
- The study consisted of:
  - a Screening Period: 2 to 3-week period from screening to inclusion
  - a Treatment Period: 12-week treatment period with nalmefene
  - a Safety Follow-up Period: 2-week period after completion of the study or after withdrawal from the study
- Alcohol consumption data were calculated using the timeline followback (TLFB),[1] which estimated the patient's alcohol intake based on standard units of 14 g alcohol/unit, which is the standard unit commonly used in Germany. Patients who had a *high* or *very high* DRL in the 4 weeks (28 days) preceding the Screening Visit and in the period between the Screening and Inclusion Visits (Screening Period) were included in the study and treated with nalmefene 18 mg as-needed use and were also provided with psychosocial support, in accordance with the European Union *Summary of Product Characteristics*.[2]

Study Methodology (continued)

- The WHO Drinking Risk Levels (DRL) of alcohol consumption is tabulated below:

Drinking Risk Level	Total Alcohol Consumption (g/day)	
	Men	Women
Low risk	1 to 40	1 to 20
Medium risk	>40 to 60	>20 to 40
High risk	>60 to 100	>40 to 60
Very high risk	>100	>60

- Between the scheduled visits, optional visits or phone calls were allowed to provide patients with psychosocial support, depending on individual patient need, at the discretion of the investigator.
- Efficacy and safety data were collected at regular intervals throughout the study.

Number of Patients Planned

60 patients were planned to be dosed with nalmefene

Diagnosis and Main Selection Criterion

Outpatients with a primary diagnosis of alcohol dependence according to DSM-IV-TR™ criteria, who:

- were ≥18 years of age with a body mass index (BMI) ≤30 kg/m^2
- had had an average alcohol consumption at *high risk* level or above (that is, >60 g of alcohol/day for men and >40 g of alcohol/day for women) in the 4 weeks preceding the Screening Visit and in the period between the Screening and Inclusion Visits
- had liver changes defined by elevated liver stiffness (>6 kPa) or elevated CAP (>215 dB/m measured by Fibroscan) at the Screening Visit
- had a breath alcohol concentration (BrAC) <0.02% at the Screening Visit
- provided a stable address and telephone number

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number

Nalmefene – 18 mg, as needed; tablets, orally; batch No. 2374069

Duration of Treatment

12 weeks

Efficacy Assessments

- TLFB
- transient elastography (Fibroscan)
- Clinical Global Impression – Severity of Illness (CGI-S)
- Clinical Global Impression – Global Improvement (CGI-I)
- 36-item Short-form Health Survey (SF-36)

Safety Assessments

- Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, waist circumference, electrocardiograms (ECGs), and physical examinations

Endpoints

- *Exploratory endpoints*:
  - Alcohol consumption:
    - change from baseline to Months 1, 2, and 3 in number of heavy drinking days (HDDs)
    - change from baseline to Weeks 1 and 2 in number of HDDs
    - change from baseline to Months 1, 2, and 3 in total alcohol consumption (TAC)
    - change from baseline to Weeks 1 and 2 in TAC
    - RSDRL response (defined as a downward shift from baseline to Month 3 in DRL; for patients at *very high risk* at baseline: a shift to *medium risk* or lower, and for patients at *high risk* at baseline: a shift to *low risk* or lower)
    - RLDRL response (defined as a downward shift from baseline to Month 3 in DRL to *low risk* or below)
    - TAC response (defined as a ≥50% or ≥70% reduction in TAC from baseline to Month 3)
    - HDD response (defined as ≤4 HDDs at Month 3)
  - Liver stiffness:
    - liver stiffness at Weeks 1, 2, 4, and 12
    - category shift from baseline to Weeks 1, 2, 4, and 12 in fibrosis stage
  - CAP:
    - CAP at Weeks 1, 2, 4, and 12
    - category shift from baseline to Weeks 1, 2, 4, and 12 in steatosis stage
  - Liver function:
    - transaminases, gamma-glutamyl transferase (GGT), bilirubin, albumin, and international normalised ratio of prothrombin (INR) at Weeks 1, 2, 4, 8, and 12
  - Clinical global impression:
    - change from baseline to Weeks 4 and 12 in CGI-S score
    - CGI-I score at Weeks 4 and 12
  - Health-related quality of life (HR-QoL):
    - change from baseline to Week 12 in the SF-36 scores
- *Safety endpoints*:
  - adverse events
  - absolute values and changes from baseline in clinical safety laboratory tests, vital signs, and weight
  - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, and weight changes

Statistical Methodology

- The following analysis sets were used:
  - *intention-to-treat set* (ITT) – all patients enrolled in the study
  - *all-patients-treated set* (APTS) – all patients in the ITT set excluding patients with no record of intake of IMP and all IMP returned
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-inclusion assessment of either an alcohol consumption variable or liver stiffness
- Demographics, baseline characteristics, medical history, and concomitant medication were summarised for the ITT; exposure was summarised for the APTS. All efficacy analyses were conducted on the FAS. All safety analyses were conducted on the APTS; pre-treatment adverse events were summarised for the ITT.
- Definition of baseline: for parameters derived from the TLFB data, baseline was defined as the month (28 days) preceding the Screening Visit. For vital signs and CGI-S, baseline was the assessment at the Inclusion Visit (Week 0). For other assessments, baseline was defined as the assessment at the Screening Visit (Week -2).
- Exposure
  - Exposure and compliance are summarised based on the APTS.
  - The number and percentage of days with IMP intake was calculated for each patient and is summarised using descriptive statistics, including percentiles (min, 10%, 25%, 50%, 75%, 90%, max), by month and in total. The number and percentage of patients in each 10% category of percentage of days with IMP intake was also summarised by month and in total.
  - Adherence to IMP was defined as days with drinking and IMP intake, no drinking and IMP intake, or no drinking and no IMP intake. Adherence to IMP was categorised as <20%, 20 to <40%, 40 to <60%, 60 to <80%, and ≥80% adherence. The number and percentage of patients in each category is summarised by month and in total. Additionally, adherence to IMP was calculated by including an additional criterion, defined as days with no IMP intake and low DRL (alcohol consumption <40 g/day for men and <20 g/day for women).
- Alcohol consumption
  - The change from baseline in monthly number of HDDs and TAC was analysed using a mixed model for repeated measurements (MMRM) using all available data until withdrawal from study, with sex, site, and time in months (1, 2, and 3) as fixed factors, and the baseline value as a covariate. The baseline value-by-time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. Least squares means for the change from baseline in monthly number of HDDs and TAC at each month was presented with two-sided 95% confidence intervals (CIs).
  - The change from baseline in weekly number of HDDs and TAC at Weeks 1 and 2 was summarised using descriptive statistics.
  - For responder endpoints, the response rates were presented with the corresponding two-sided 95% CIs using normal approximation, based on observed data.
- Liver stiffness
  - The log-transformed value of liver stiffness was analysed using an MMRM model with sex, site, and time in weeks as fixed factors, and the log-transformed baseline score as a covariate. The log-transformed baseline value-by-time interaction was also included in the model. An unstructured covariance structure was used to model the within-patient errors. The adjusted mean was back-transformed using the exponential function and presented as geometric mean.
  - Shifts from baseline in fibrosis stage (0, 1-2, 3, or 4) at every visit were summarised using descriptive statistics.
  - Subgroup analysis of liver stiffness were performed for patients with AST and ALT <100 U/L or ≥100 U/L at baseline.

Statistical Methodology (continued)

- CAP
  - CAP was analysed using the same methodology as described for the alcohol consumption endpoints, HDDs and TAC, with time in weeks in the model.
  - Shifts from baseline in steatosis stage (S0, S1, S2, or S3) at every visit was summarised using descriptive statistics where: S0: ≥100 and <215 dB/m, S1: ≥215 and <252 dB/m, S2: ≥252 and <296 dB/m, and S3: ≥296 dB/m.
- Liver function
  - Log-transformed values of transaminases, GGT, bilirubin, albumin, and INR were analysed using the same methodology as for liver stiffness.
- Associations between reduction of alcohol consumption, liver stiffness, CAP, and liver enzymes
  - The associations between reduction of alcohol consumption, liver stiffness, CAP, and liver enzymes at Weeks 1, 2, 4, and 12 were explored using a scatter plot matrix with or without estimated regression lines.
  - The associations were also explored using mixed models with log liver parameters as response and reduction in TAC as the exploratory variable, and adjusting for parameters which may affect the results. The parameters adjusted were: sex, site, week, family alcohol history, age, age at first drinking, BMI, and the individual baseline log liver parameters. The log likelihood ratio test was used to select the final model for each liver parameter.
- Clinical global impression
  - The change from baseline in CGI-S score was analysed using the same methodology as described for the alcohol consumption endpoints, HDDs and TAC.
  - CGI-I was analysed using the same methodology as described for the alcohol consumption endpoints, HDDs and TAC, with screening CGI-S score as a covariate.
- HR-QoL
  - The change from baseline in SF-36 was summarised using descriptive statistics.
- Safety
  - The overall incidences of adverse events, serious adverse events (SAEs), and adverse events leading to withdrawal were summarised. The incidences of treatment-emergent AEs (TEAEs), SAEs, and AEs leading to withdrawal were summarised by primary system organ class (SOC) and preferred term.
  - Absolute values and changes from baseline in each safety variable were summarised by visit and for the last assessment. All available assessments were included in the identification of the last assessment (scheduled, re-assessments, and unscheduled).
  - The number and percentage of patients with at least one PCS value at any post-baseline (Screening Visit) assessment time point are summarised for each safety variable. All available assessments were included in the evaluation of PCS values (scheduled, re-assessments, and unscheduled).
  - For patients with post-baseline PCS values, listings are provided including all the values for those patients for the variable, with flagging of PCS values and out-of-reference-range values.
  - All adverse events for patients with PCS values were listed by screening number, and include the PCS value plus the value for that variable at all other assessment timepoints.
  - The absolute values of GGT, bilirubin, albumin, ALT, AST, and INR were presented graphically by visit and last assessment using box plots and with all available assessments using patient line plots. All PCS values were marked in the plot. Reference lines for PCS limits were also included. If more than one value was available at a given assessment time point, the maximum value was used in the plots.

Patient Disposition and Analysis Sets

- Patient disposition is summarised below:

	Nalmefene	
	n	(%)
Patients enrolled (ITT)	45	
Patients treated (all-patients-treated set [APTS])	45	
Patients completed	39	(86.7)
Patients withdrawn	6	(13.3)
Primary reason for withdrawal:		
Adverse event(s)	2	(4.4)
Withdrawal of consent	2	(4.4)
Lost to follow-up	2	(4.4)
Analysis sets:		
ITT	45	
APTS	45	
Full-analysis set (FAS)	45	

Cross reference: Tables 1 and 3
Patient disposition by site is summarised in Table 2.
Withdrawals by all reason is summarised in Table 4 and all withdrawals from the study are in Listing 1

Demography and Baseline Characteristics of the Study Population

- All patients were White, with a mean age of 59 years (range: 33 to 75 years), and slightly more men than women were enrolled (56% *versus* 44%; Table 5).
- Baseline alcohol consumption and liver status are summarised in Tables 6 and 7, respectively. Except for 1 patient who had *medium* DRL, the remaining patients had either *high* DRL (40%) or *very high* DRL (58%) at baseline. The mean HDD and TAC was 26 HDDs/month and 98 g/day, respectively. All patients had elevated CAP and approximately half of them also had elevated liver stiffness.
- Baseline weight, BMI, and waist circumference are summarised by sex in Table 8. Approximately half of the women and half of the men were overweight; the median BMI was 24.6 kg/m^2 and 25.7 kg/m^2 for women and men, respectively. In addition, the mean waist circumference of 89 and 100 cm in women and men, respectively, reflects abdominal adiposity.
- Alcohol-related histories are summarised in Tables 9 to 11. The mean age at first experience of drinking was 16 years and the mean age at onset of drinking problems was 47 years (Table 9). In patients who had been treated for alcohol problems (13 patients), the mean age at treatment for drinking problems was 49 years (Table 11). The majority of the patients had sought help from Alcoholics Anonymous or other self-help groups (73% and 80%, respectively) for their drinking problems (Table 11).
- 40% of the patients were current/former smokers (Table 12). A similar proportion of patients were either employed or retired (42% and 40%, respectively; Table 13) and the majority of the patients did not have a familial history of psychiatric disorders (Table 14).
- The majority (89%) of the patients had normal ECG results at screening. None of the patients had abnormal and clinically significant ECG results; 5 patients had abnormal but not clinically significant ECG results (Table 15).

Demography and Baseline Characteristics of the Study Population (continued)

- Approximately 78% of the patients had concurrent medical, neurological, or psychiatric disorders (Table 16). The most common (>20%) concurrent disorders (by SOC) were: vascular disorders (38%; all patients had *hypertension*), metabolism and nutrition disorders (27%), musculoskeletal and connective tissue disorders (24%; mainly *osteoarthritis*), and psychiatric disorders (24%; mainly *depressive symptom*).
- Recent and concomitant medications taken by patients is summarised in Tables 17 (discontinued prior to inclusion), 18 (continued after inclusion), and 19 (started at/after inclusion). The most common therapeutic classes of medication (≥5 patients) continued after inclusion were: *β-blocking agents* (11 patients; mainly bisoprolol), *lipid modifying agents* (7 patients; mainly simvastatin), *thyroid preparations* (7 patients; mainly levothyroxine sodium), *ACE inhibitors, plain* (6 patients), *antidepressants* (6 patients), *antigout preparations* (5 patients), *antiinflammatory and antirheumatic products* (5 patients), and *antithrombotic agents* (5 patients; mainly acetylsalicyclic acid). The most common therapeutic classes of medication (≥3 patients) started at/or after inclusion were *analgesics* and *psycholeptics* (3 patients each).

Exposure

- Exposure is summarised in Tables 20 to 24. Treatment compliance is summarised in Tables 25 to 29 and treatment compliance which included an additional criterion, defined as days with no IMP intake and low DRL, are summarised in Tables 30 to 34.
- On average, patients took IMP on 55% of the days (Table 21). When the percentage of days with IMP intake is summarised in 10% categories, the greatest proportion of patients either took IMP on ≤10% of the days or on >90% of the days (approximately 16% and 29%, respectively; Table 21). The mean percentage of days with IMP intake decreased from Month 1 to Month 3 (62% and 48%, respectively; Table 23).
- On average, patients adhered to treatment on 70% of the days (Table 26). Overall, approximately half of the patients were ≥80% compliant with IMP; the proportion of patients who were ≥80% compliant with IMP decreased from Month 1 to Month 3 (56% to 44%, respectively; Table 29). Similar results were obtained when adherence to IMP was analysed by including an additional criterion, days with no IMP intake and low DRL (Table 34).

Efficacy Results

Alcohol Consumption

- The HDD and TAC results are summarised below (FAS, OC, MMRM):

	Baseline		Adjusted Change from Baseline				95% CI	
	N	Mean	Month	N	Mean	SE	Lower	Upper
Number of HDDs	44	26.1	1	44	-12.7	1.4	-15.6	-9.8
			2	40	-13.1	1.5	-16.2	-10.2
			3	38	-13.5	1.7	-16.9	-10.2
TAC (g/day)	44	97.9	1	44	-42.4	5.4	-53.4	-31.4
			2	40	-42.9	5.6	-54.2	-31.5
			3	38	-45.8	6.4	-58.6	-33.0

CI = confidence interval; SE = standard error
Cross-reference: Tables 37 and 40
Absolute values of HDD and TAC are in Tables 35 and 38, respectively.
Changes from baseline in HDD and TAC are in Tables 36 and 39.

- In the MMRM, OC analysis, the monthly number of HDDs and TAC decreased during the treatment period. The change from baseline to Month 1 in number of HDDs and TAC was -12.7 HDDs and -42.4 g/day, respectively. Sustained reductions with slight improvements, were observed at Months 2 and 3.

Efficacy Results (continued)

- The mean weekly number of HDDs and TAC at screening was 6.4 HDDs and 98.5 g/day, respectively (Tables 41 and 43). Reduction in alcohol consumption was already observed at Week 1, with change from baseline of -2.8 HDDs and -39.2 g/day, respectively (Tables 42 and 44). Similar results were obtained at Week 2.
- 38% of the patients were RSDRL responders, that is, the patients had a downward shift from baseline to Month 3 in DRL (Table 45). Similarly, 33% of the patients were RLDRL responders, that is, the patients had a downward shift from baseline to Month 3 in DRL to *low risk* or below (Table 46).
- TAC response, defined as a ≥50% or ≥70% reduction in TAC at Month 3 is summarised in Tables 47 and 48, respectively. 49% and 23% of the patients had a TAC response of ≥50% or ≥70%, respectively.
- HDD response, defined as having ≤4 HDDs at Month 3 is summarised in Table 49. 31% of the patients were HDD responders.

Liver Stiffness

- The results of liver stiffness assessment are summarised in Tables 50 and 51. Per inclusion criterion, approximately half of the patients included in this study had slightly elevated liver stiffness at screening, as indicated by geometric mean of 7.0 kPa (Table 50). At Month 3, the geometric mean of liver stiffness was 6.0 kPa (Table 51).
- Shifts in fibrosis stage are summarised in Table 52. In general, the fibrosis stage remained unchanged in the majority of the patients at Month 3. A total of 8 patients shifted to a lower (better) fibrosis stage at Month 3: 4 patients shifted from stage F1-2 to F0, 3 patients shifted from stage F3 to F1-2 or F0, and 1 patient shifted from stage F4 to F0. A total of 5 patients shifted to a higher (worse) fibrosis stage at Month 3: 2 patients shifted from stage F0 to F1-2, 2 patients shifted from stage F1-2 to F3, and 1 patient shifted from stage F3 to F4.
- Subgroup analysis of liver stiffness for patients with AST and ALT <100 IU/L or ≥100 IU/L at baseline was not performed as only 1 patient had AST and ALT ≥100 IU/L (Table 53).

CAP

- Hepatic steatosis was assessed via CAP and the results are summarised in Tables 54 and 55. All patients had elevated CAP at baseline (Table 7); during the treatment period, the mean CAP value decreased from geometric mean of 295 Db/m at baseline to 265 Db/m at Month 3 (Table 55).
- Shifts in steatosis stage are summarised in Table 56. In general, the steatosis stage remained unchanged in the majority of the patients at Month 3. A total of 13 patients shifted to a lower (better) steatosis stage at Month 3: 2 patients shifted from stage S1 to S0, 4 patients shifted from stage S2 to ≤S1, and 7 patients shifted from stage S3 to ≤S2. A total of 5 patients shifted to a higher (worse) steatosis stage at Month 3: 1 patient shifted from stage S1 to S2 and 4 patients shifted from stage S2 to S3.

Liver Function

- Liver function was assessed by measuring levels of transaminases, GGT, bilirubin, albumin, and INR and the results are summarised in Tables 57 to 68 for the individual parameters. Reductions in transaminases and GGT values were observed, starting from Week 1 through to Month 3. The mean values of bilirubin, albumin, and INR were unchanged at Month 3.

Associations Between Reduction in Alcohol Consumption and Liver Parameters

- The associations between reduction of alcohol consumption, liver stiffness, CAP, and liver enzymes are summarised in Tables 69 to 72 and presented in Figures 1 to 4. In general, greater reduction in alcohol consumption corresponds to reduction (improvement) in liver stiffness, CAP, and liver enzymes, that is, there was a modest negative association between reductions in alcohol consumption with these liver parameter values. The correlation estimates at Month 3 ranged from -0.44 (for AST) to -0.23 (for liver stiffness; Table 72).
- The results of the mixed models analyses are in *Key Statistical Output*. The final model for each liver parameter included week and the individual baseline log liver parameter values. For CAP, the final model also included BMI and for transaminases and GGT values, the final model also included the interaction between reduction in TAC and week. For every unit decrease in TAC, there was a slight decrease (improvement) in the parameter values of liver stiffness, CAP, ALT, AST, and GGT.

Efficacy Results (continued)

Clinical Global Impression

- The results of CGI-S score are summarised in Tables 73 to 75. The mean CGI-S score was 3.9 points at baseline and decreased to 2.7 points at Month 3 (Table 73); the adjusted change from baseline to Month 3 in CGI-S score indicated an improvement of 1.0 points (Table 75).
- The results of CGI-I score are summarised in Tables 76 and 77. The adjusted mean CGI-I score was 2.8 and 2.6 points at Months 1 and 3 (Table 77), respectively, indicating that patients were *minimally* to *much improved*.

HR-QoL

- HR-QoL was assessed using SF-36 and the mental and physical component summary scores are summarised in Tables 78 and 79 and Tables 80 and 81, respectively. The scores range from 0 to 100, with higher scores indicating better quality of life.
- The mean mental and physical component summary scores at screening were approximately 43 and 52 points, respectively, (Tables 78 and 80). At Month 3, the mental component summary score indicated an improvement while the mean physical component summary score was relatively unchanged; the mean change from baseline in mental and physical component summary score was 4.1 and 1.2 points, respectively (Tables 79 and 81).

Safety Results

Adverse Events

- All pre-dose adverse events with onset prior to IMP administration are summarised in Table 82 and listed in Listing 2. Three patients had pre-dose adverse events; all events were non-serious and all patients recovered from the events (Listing 2).
- The adverse event incidence is summarised below:

	Nalmefene	
	n	(%)
Patients treated	45	
Patients who died	0	(0)
Patients with treatment-emergent serious AEs (SAEs)	3	(6.7)
Patients with treatment-emergent adverse events (TEAEs)	34	(76)
Patients with AEs leading to withdrawal	3	(6.7)
Total number of SAEs	3	
Total number of TEAEs	141	
Total number of AEs leading to withdrawal	7	

Cross-reference: Table 83

- TEAEs are summarised by SOC and preferred term in Table 84, by preferred term in Table 85, and by intensity in Table 87. TEAEs considered *related* to IMP are summarised by SOC and preferred term in Table 88 and by intensity in Table 89. SAEs are summarised in Tables 90 and 91 and listed in Listing 3. TEAEs leading to withdrawal are summarised in Tables 92 and 93 and listed in Listing 4.
- Overall, 76% of the patients had at least one TEAE. The proportion of patients who had TEAEs considered *related* to IMP was 69% (Table 88). The majority of the patients with *related* TEAEs had *mild* or *moderate* events (Table 89); *severe*, *related* TEAEs were single events reported in individual patients (Table 89).
- A total of 3 patients had 3 SAEs: vomiting, alcohol detoxification, and joint injury (Tables 90 and 91); two of the SAEs (vomiting and alcohol detoxification) were considered *related* to IMP by the investigators; none of the SAEs led to withdrawal and all patients recovered from the events (Listing 3). For further details, refer to the individual narratives in *Narratives of Serious Adverse Events and Adverse Events Leading to Withdrawal*.

Safety Results (continued)

- A total of 3 patients had 7 adverse events leading to withdrawal. Except for dizziness (2 patients), all adverse events leading to withdrawal were single events reported in individual patients (Tables 92 and 93). None of the adverse events leading to withdrawal were serious (Listing 4). For further details, refer to the individual narratives in *Narratives of Serious Adverse Events and Adverse Events Leading to Withdrawal*.
- TEAEs with an incidence ≥5% are summarised below:

Preferred Term (MedDRA Version 16.1)	Nalmefene n	(%)
Patients treated		
Dizziness	14	(31.1)
Fatigue	9	(20.0)
Insomnia	9	(20.0)
Nausea	9	(20.0)
Headache	6	(13.3)
Diarrhoea	5	(11.1)
Restlessness	5	(11.1)
Vomiting	5	(11.1)
Malaise	4	(8.9)
Paraesthesia	4	(8.9)
Dyshidrotic eczema	3	(6.7)
Hyperhidrosis	3	(6.7)

Cross-reference: Table 86

Clinical Safety Laboratory Tests

- The reference ranges and PCS definitions are in Table 94. The laboratory values and the changes relative to baseline are summarised in Tables 95 to 101 and Tables 102 to 108, respectively.
- The mean changes from baseline to Month 3 in laboratory values were small and not considered clinically relevant (Tables 102 to 108).
- The incidences of post-baseline PCS laboratory values are summarised in Tables 109 to 115. The patients with PCS laboratory values are in Listing 5 and adverse events in patients with PCS laboratory values are in Listing 6. Post-baseline PCS laboratory values with an incidence ≥10% were: PCS high fasting cholesterol (49%), PCS high fasting glucose (36%), PCS high GGT (24%), PCS high fasting triglycerides (11%), and PCS high urea nitrogen (11%). The patients generally had isolated post-baseline PCS laboratory values; at least one of the post-baseline cholesterol and GGT values were PCS also at baseline in ≥60% of the patients (Listing 6). None of the patients who had PCS laboratory values had a corresponding TEAE, except 1 patient who had PCS high transaminases and GGT (*hepatitis alcoholic*; Listing 6); the event was considered *related* to IMP by the investigator and the patient recovered from the event (Listing 2).
- To exclude other aetiologies of liver fibrosis, ferritin, iron, and transferrin were assessed at the Screening Visit only. Except for ferritin, the mean values of iron and transferrin were within the respective reference ranges (Table 98). PCS values of these three laboratory parameters were observed in some patients; none of the patients had a corresponding TEAE (Listing 6). The elevated levels were assessed by the investigator to be related to the patients' alcoholic liver disease.
- The results of serology and urinalysis are summarised in Tables 116 and 117, respectively. The serology and urinalysis results did not show any clinically relevant changes during the study.

Safety Results (continued)

Vital Signs

- The reference ranges and PCS definitions are in Table 94. The vital signs values and the changes relative to baseline are summarised in Tables 118 and 119, respectively. The mean vital signs values were within the reference ranges at all scheduled timepoints. The mean changes from baseline to Month 3 in systolic and diastolic blood pressure were -4.6 and -1.1 mmHg, respectively.
- The incidences of post-baseline PCS vital signs values are summarised in Table 120. The patients with PCS vital signs values are in Listing 7 and adverse events in patients with PCS vital signs values are in Listing 8. PCS high diastolic and systolic blood pressure was reported in 1 patient each (2.3%) without any corresponding TEAE (Listing 8).

Weight and Waist Circumference

- The PCS definitions are in Table 94. The weight and waist circumference and the changes relative to baseline are summarised in Tables 121 and 122, respectively. The mean weight and waist circumference was stable during the study.
- The incidences of post-baseline PCS weight changes are summarised in Table 123. The patients with PCS weight changes are in Listing 9 and adverse events in patients with PCS weight changes are in Listing 10. A total of 2 patients had PCS weight changes: one patient had PCS weight increase and the other patient had PCS weight decrease; neither patients had any corresponding TEAE (Listing 10).

Physical and Neurological Examinations

- The physical and neurological examination findings are summarised in Tables 124 and 125, and Tables 126 and 127, respectively. The majority of the physical and neurological findings were considered normal at baseline and during the study.

Discussion

- Studies have shown that complete alcohol abstinence can significantly decrease liver stiffness (LS) and CAP.[3,4] However, there are insufficient data to demonstrate if similar beneficial effects are observed by reducing alcohol consumption in patients with liver impairment. Moreover, there is a shortage of data on how much and how long alcohol consumption needs to be reduced and maintained to see an effect on liver stiffness and CAP.
- In concordance with the label population (patients who had at least a *high* DRL)[5] in the nalmefene phase III studies, approximately 50% reductions in TAC and HDD were observed at Month 3 in patients with liver impairments. In addition, the patients' liver enzymes values were reduced and a trend towards improvements were also observed in the surrogate markers of liver harm, namely, LS and CAP which decreased by 1 kPa and 30 dB/m, respectively. Since LS reflects both the degree of fibrosis and inflammation, the slight improvement of LS over the 3-month treatment period is most likely due to resolution of inflammation.[6] It is not expected that reduction of drinking levels over a short period of three months will result in a change of fibrosis stage since it usually takes more than 10 years to develop cirrhosis.[7] Indeed, fibrosis stages as assessed using AST-adapted cut off values of LS[8] were generally unchanged during the treatment period.
- Although the small change in LS is most likely a reflection of a decrease in inflammation, a modest association that greater reduction in TAC resulted in improvement in LS and CAP was nevertheless shown. It is expected that a longer observation period is required in order to see a more pronounced and clinically meaningful reduction of liver fibrosis or steatosis. Recent data indicate that LS elevation *per se* during drinking periods are an indication of later fibrosis progression and in at-risk patients, it is also an indication of further progression to cirrhosis. Taken together, the effect of alcohol consumption on LS becomes more evident if patients with more severe stage of liver disease are studied, for example, patients with Child-Pugh A cirrhosis.[8] Therefore, the findings in this exploratory study in a patient population with less severe hepatic impairment are not unexpected and certainly deserve further investigation.
- The results of liver biochemistry showed that a number of patients had elevated levels of cholesterol and triglycerides, which is not unusual in heavy drinkers since alcohol is known to affect lipid metabolism. Elevated levels of transaminases and GGT were also observed and are to be expected in patients with alcohol use disorder and liver impairment.

Conclusions

- In alcohol dependent patients with liver impairment, treatment with nalmefene for 3 months reduced their TAC and the number of HDD by approximately 50% relative to baseline.
- After 3 months of treatment with nalmefene, no clear reduction in liver stiffness was seen.
- However, a reduction in CAP was observed.
- The liver enzymes values improved minimally and the fibrosis stage remained largely unchanged.
- A modest negative associations were observed between reduction in alcohol consumption and improvements in liver stiffness, CAP, and liver enzymes.
- Concurrent with reductions in alcohol consumption, improvements were observed in the severity of patients' condition and patients' self-reported outcome in mental QoL.
- Nalmefene was safe and well tolerated and no new safety concerns were observed.

Report Date

22 April 2016

This study was conducted in compliance with the principles of *Good Clinical Practice*.