

Synopsis – Study 15892A

<p>Study Title Interventional, open-label study of 18 mg Selincro[®] as needed use, in the treatment of patients with alcohol dependence in primary care</p>
<p>Investigators 43 principal investigators at 43 sites in 4 countries <i>Signatory investigator</i> – [REDACTED]</p>
<p>Study Sites 43 sites – 8 in France, 11 in Germany, 13 in Spain, and 11 in the United Kingdom</p>
<p>Publications None (as of the date of this report)</p>
<p>Study Period <i>First patient first visit</i> – 5 August 2014 (the date when the first <i>Informed Consent Form</i> was signed) <i>Last patient last visit</i> – 11 February 2016 (the date of the planned last protocol-specified contact with any patient) <i>Study terminated</i> – 25 September 2015</p>
<p>Objectives</p> <ul style="list-style-type: none"> • <i>Primary objective:</i> <ul style="list-style-type: none"> – to determine the reduction in alcohol consumption in patients with alcohol dependence treated with 18 mg Selincro[®] as-needed use, in conjunction with continuous psychosocial support in primary care (Cohort A) • <i>Secondary objectives:</i> <ul style="list-style-type: none"> – to evaluate the change in patients treated with 18 mg Selincro[®] as-needed use, on: <ul style="list-style-type: none"> • clinical status • liver function • quality of life • <i>Exploratory objectives:</i> <ul style="list-style-type: none"> – to determine the reduction in alcohol consumption in patients with alcohol dependence who reduce their alcohol consumption to below a <i>high</i> drinking risk level (according to the World Health Organization [WHO]) in the screening period (and are therefore not eligible for Selincro[®] (nalmefene) treatment according to the <i>Summary of Product Characteristics (SmPC)</i>) (Cohort B) – to evaluate the psychometric properties of the Alcohol Quality of Life Scale (AQoLS) • <i>Safety objective:</i> <ul style="list-style-type: none"> – to evaluate the safety and tolerability of 18 mg Selincro[®] as-needed use, in primary care

Study Methodology

- This was an interventional, multi-national, multi-site, open-label study with nalmefene, as-needed use.
- The study consisted of 2 cohorts, A and B. The patients' clinical status, alcohol dependence, social and family situation, alcohol consumption, and treatment goal were assessed at the Screening Visit (Visit 1). Thereafter, the patients were asked to record their alcohol consumption for approximately 2 weeks until the Inclusion Visit (Visit 2). The Timeline Follow-back (TLFB) method was used to collect information about the patients' alcohol consumption. Alcohol intake was reported in standard units (based on individual country's definitions of a standard unit), and conversion from standard unit to g alcohol/day was done.
- Cohort A comprised patients who maintained a *high* drinking risk level (DRL, defined by WHO as >60g alcohol/day for a man or >40g alcohol/day for a woman), or above, in the period between the Screening and Inclusion Visits. In Cohort A, the total study duration per patient from screening to the end of follow-up was approximately 16 weeks and comprised a 2-week Screening Period, a 12-week Treatment Period, and a 2-week Safety Follow-up Period. Visit 3 took place 1 week after the Inclusion Visit, and to mimic routine clinical practice, investigators were given some flexibility in scheduling Visits 3, 4, 5, and 6 (that is, Visit 3 was to take place 4 to 10 days after Visit 2; Visits 4, 5, and 6 were to take place at ± 1 week of Weeks 4, 8, and 12, respectively). The Safety Follow-up Visit (Visit 7) was to be scheduled 2 weeks after Visit 6. Psychosocial support was administered by site personnel throughout the study; it did not include any formal, manual-guided psychosocial intervention, but included key elements of motivational interviewing with focus on alcohol reduction and treatment adherence.
- Cohort B comprised patients who reduced their alcohol consumption in the period between the Screening and Inclusion visits, that is, patients who did not maintain at least a *high* DRL at the Inclusion Visit (and were therefore not eligible for treatment with Selincro[®] according to the SmPC). In Cohort B, the total study duration per patient from screening to the end of follow-up was approximately 14 weeks and comprised a 2-week Screening Period and a 12-week Observational Period. Visit 3, which is the Completion Visit, took place 12 weeks after the Inclusion Visit. At the Completion Visit, TLFB, global clinical status, treatment modalities, concomitant medication, and adverse events were collected. Psychosocial support at the Inclusion Visit focused on encouraging the patients to maintain their reduced alcohol consumption.
- Patients who withdrew from the study were to be seen for a withdrawal visit as soon as possible after they withdrew.
- The study was terminated due to difficulties in patient recruitment and due to difficulties in study initiation in Italy leading to significant delay in the conduct of the study. All ongoing patients at the time of study termination were allowed to complete the study.

Number of Patients Planned

635 patients were planned for inclusion in the study: 475 in Cohort A (treatment with Selincro[®]) and 160 in Cohort B (treatment without Selincro[®]). Five countries were planned in this study, and in each country, 95 patients were planned for inclusion in Cohort A and 32 patients were planned for inclusion in Cohort B.

Diagnosis and Main Selection Criterion

Outpatients with a primary diagnosis of alcohol dependence according to ICD-10 criteria, who:

- had a *high* DRL in the 4 weeks preceding the Screening Visit
- were ≥ 18 years of age
- provided a stable address and telephone number

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

Nalmefene – 18 mg; as needed; tablets, orally; batch Nos. 2374069 and 2408451

Duration of Treatment

12 weeks

Efficacy Assessments

- Number of heavy drinking days (HDDs)
- Total alcohol consumption (TAC)
- Response based on various drinking measures (please refer to the *Endpoints* section below)
- Clinical Global Impression – Global Improvement (CGI-I)
- Clinical Global Impression – Severity of Illness (CGI-S)
- γ -glutamyltransferase (GGT)
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- 36-item Short-form Health Survey, version 2 (SF-36)
- AQoLS

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/body mass index (BMI), and physical examinations

Endpoints**For Cohort A:**

- *Primary endpoint:*
 - change from baseline to Month 3 in the number of HDDs (days/month)
- *Secondary endpoints:*
 - change from baseline to Month 3 in TAC (g/day)
 - RSDRL response; defined as a downward shift from baseline to Month 3 in DRL; for patients with a *very high* DRL at baseline, a shift to *medium* DRL or below; for patients with a *high* DRL at baseline, a shift to *low* DRL or below
 - RLDRL response; defined as a downward shift from baseline to Month 3 in DRL to *low* DRL or below
 - Response (R70): defined as $\geq 70\%$ reduction in TAC from baseline to Month 3
 - Response (R50): defined as $\geq 50\%$ reduction in TAC from baseline to Month 3
 - Response (R0): defined as 0 to 4 HDDs (days/month) at Month 3
 - change from baseline to Week 12 in CGI-S score
 - CGI-I at Week 12
 - GGT, ALT, and AST at Week 12
 - change from baseline to Week 12 in SF-36 Physical Component Summary and Mental Component Summary scores (only for patients in France and the United Kingdom)
- *Exploratory endpoint:*
 - change from baseline to Week 12 in AQoLS total score (only for patients in France and the United Kingdom)
- *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

For Cohort B:

- *Exploratory endpoints:*
 - change from baseline to Month 3 in the number of HDDs (days/month)
 - change from baseline to Month 3 in TAC (g/day)
- *Safety endpoints:*
 - adverse events

Statistical Methodology

- The following analysis sets were used to analyse and present the data for Cohort A:
 - *all-patients-in-Cohort-A set* (APAS) – all patients enrolled in Cohort A
 - *all-patients-treated set* (APTS) – all patients in the APAS excluding those with no recorded investigational medicinal product (IMP) intake
 - *full-analysis set* (FAS) – all patients in the APAS who had at least one valid post-inclusion assessment of the primary efficacy variable (HDDs)
- The following analysis sets were used to analyse and present the data for Cohort B:
 - *all-patients-in-Cohort-B set* (APBS) – all patients enrolled in Cohort B
- For Cohort A, disposition, demographics, and baseline characteristics were based on the APAS. The primary, secondary and exploratory efficacy analyses were based on the FAS. Safety analyses, tabulations of recent and concomitant medications, and exposure were based on the APTS.
- For Cohort B, disposition, demographics, and baseline characteristics were based on the APBS. Efficacy and safety analyses were also based on the APBS.
- For the parameters derived from TLFB, 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. For other assessments, baseline was defined as the assessment at the Screening Visit.
- *Exposure:*
 - The number and percentage of days with IMP intake in Cohort A were calculated for each patient and summarised using descriptive statistics. The number and percentage of patients in each 10% category of percentage of days with IMP intake were also summarised by month and in total.
 - Adherence days were defined as days with drinking and with IMP intake, no drinking and with IMP intake, or no drinking and with no IMP intake.
 - Adherence to IMP was categorised based on <20%, 20–<40%, 40–<60%, 60–<80%, and ≥80% adherence. The number and percentage of patients in each category were summarised by month and in total. An alternative adherence to IMP calculation was presented by including an additional criterion, that is, no IMP intake and alcohol consumption <40 g/day for men and <20 g/day for women.
- *Analysis of the primary endpoint:*
 - The change from baseline to Month 3 in the number of HDDs (days/month) in Cohort A was analysed using a mixed model for repeated measurements (MMRM), using all available observations until completion or withdrawal from the study. The model included sex, site, and time in months (Months 1 to 3) as fixed categorical effects, baseline number of HDDs as a continuous covariate, and baseline number of HDDs-by-month interaction. An unstructured covariance structure was used to model the within-patient errors and the estimation method used a restricted maximum likelihood (REML)-based approach. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The adjusted mean change from baseline in number of HDDs at each month was presented with two-sided symmetric 95% confidence intervals and corresponding p-values. The null hypothesis of no treatment effect (that is, no change from baseline) was tested at the 5% level of significance.
 - A sensitivity analysis of the primary endpoint was performed using an analysis of covariance (ANCOVA) model using last observation carried forward (LOCF), including sex, site, and time in months as fixed effects, baseline number of HDDs as a continuous covariate, and baseline number of HDDs-by-month interaction.
 - Subgroup analyses by country for the change from baseline in number of HDDs in Cohort A were performed on an exploratory basis, using the same methodology as that for the total Cohort A.

Statistical Methodology (continued)

- *Analysis of the secondary endpoints:*
 - TAC, CGI-S, CGI-I, and the liver parameters (GGT, ALT, and AST) for Cohort A were analysed using the same methodology as that described for the primary endpoint. In the analysis of CGI-I, the CGI-S score at the Screening Visit was used as baseline. In the analysis of liver parameters, log transformed GGT, ALT, and AST were used as response variables. The change from baseline to Week 12 in SF-36 physical component score and mental component score were analysed using an ANCOVA model with missing values imputed by LOCF, including sex and site as fixed effects, and baseline score as a covariate.
 - Subgroup analyses by country for the change from baseline in TAC (g/day) were performed on an exploratory basis, using the same methodology as that for the total Cohort A.
 - For responder endpoints (all derived based on TLFB data) for Cohort A, the percentage of responders were presented with corresponding two-sided 95% confidence intervals based on a normal approximation, using observed data.
- *Analysis of the exploratory endpoints:*
 - The change from baseline in HDDs and TAC for Cohort B were summarised descriptively, using observed data.
 - The change from baseline in AQoLS total score was summarised descriptively, using observed data. The psychometric properties of the AQoLS will be evaluated in a separate report.
- *Safety:*
 - The overall incidences of adverse events, serious adverse events (SAEs), and adverse events leading to withdrawal were summarised by preferred term for Cohort A and Cohort B separately. All adverse events were listed for Cohort A and Cohort B separately. For patients in Cohort A, adverse events were classified according to when the adverse event started:
 - *pre-treatment adverse event* – an adverse event that starts when or after the patient signed the *Informed Consent Form* and prior to the date of first dose of IMP
 - *treatment-emergent adverse event (TEAE)* – an adverse event that starts on or after the date of first dose of IMP and prior to the last protocol-specified contact with that patient
 - Descriptive statistics for the safety variables, both absolute values and changes from baseline, were presented by visit and the last assessment. Unless otherwise specified, tables and listings for Cohort A were based on the APTS; tables and listings for Cohort B were based on the APBS.

Patient Disposition and Analysis Sets

- Patient disposition is summarised below:

	Cohort A		Cohort B	
	n	(%)	n	(%)
Patients enrolled	330		48	
Patients completed	268	(81.2)	47	(97.9)
Patients withdrawn	62	(18.8)	1	(2.1)
Primary reason for withdrawal:				
Adverse event(s)	18	(5.5)	1	(2.1)
Lack of efficacy	1	(0.3)	0	(0)
Withdrawal of consent	21	(6.4)	0	(0)
Other	22	(6.7)	0	(0)
Analysis sets:				
All-patients-in-Cohort-A set (APAS)	330		NA	
All-patients-treated set (APTS)	311		NA	
Full-analysis set (FAS)	301		NA	
All-patients-in-Cohort-B set (APBS)	NA		48	

NA = Not applicable

Cross-reference: Tables 1, 3, 5, and 7

Patient disposition by site is summarised in Tables 2 and 6. Withdrawals by all reason is summarised in Tables 4 and 8, and all withdrawals from the study are in Listings 5 and 9.

Demography and Baseline Characteristics of the Study Population

Cohort A:

- In Cohort A, 65% of the patients were men (Table 9). The mean age was approximately 52 years (range: 21 to 84 years) and almost all (99%) patients were White. The mean baseline BMI of men and women were 27.9 and 26.3 kg/m², respectively (Table 10).
- At the Screening Visit (baseline), the mean number of HDDs and TAC among patients in Cohort A was 24 days/month and 111 g/day, respectively, and the mean CGI-S score was 4.0 (Table 11). The mean baseline GGT, ALT, and AST levels were 120, 35, and 40 IU/L, respectively (Table 12). At the Inclusion Visit, the mean number of HDDs and TAC among patients in Cohort A was 24 days/month (Table 13) and 106 g/day (Table 14), respectively.
- Among patients in Cohort A, the mean age at onset of drinking problems was 37 years (Table 15), and the mean age at first treatment for drinking problems was 42 years (Table 16). Most patients (74%) had never been treated for alcohol dependence. Approximately half (53%) of the patients had a family history of alcohol problems (Table 17), and most patients (80%) smoked (Table 18). Approximately half (45%) of the patients were under paid employment or self-employed (Table 19).
- Apart from alcohol dependence, 85% of the patients in Cohort A had concurrent psychiatric, neurological, or other significant medical disorders (Table 30). The most common (≥10%) concurrent disorders (by preferred term) were: *hypertension* (33%), *depressive symptom* (13%), *type 2 diabetes mellitus* (11%), and *hypercholestromia* (10%). Approximately 14% of the patients had a concomitant medication discontinued prior to study inclusion (Table 31) and approximately 74% of the patients had a concomitant medication continued after study inclusion (Table 32). Approximately 38% of the patients started a concomitant medication at or after study inclusion (Table 33), and the most common Anatomical Therapeutic Chemical (ATC) classification system Level 3 group of medications prescribed were *antiinflammatory and antirheumatic products* (7%).

Cohort B:

- In Cohort B, 81% of patients were men (Table 20). The mean age was approximately 55 years (range: 28 to 83 years) and almost all (98%) patients were White. The mean baseline BMI of men and women were 28.4 and 24.3 kg/m², respectively (Table 21).
- At the Screening Visit (baseline), the mean number of HDDs and TAC among patients in Cohort B was 23 HDDs/month and 84 g/day, respectively (Table 22). At the Inclusion Visit, the mean number of HDDs and TAC among patients in Cohort B was 5 days/month (Table 23) and 31 g/day (Table 24), respectively. The substantially different mean number of HDDs and TAC between Cohorts A and B at the Screening Visit reflects the different treatment management needs between the 2 cohorts.
- Among patients in Cohort B, the mean age at onset of drinking problems was 40 years (Table 25), and the mean age at first treatment for drinking problems was 44 years (Table 26). Most patients (77%) had never been treated for alcohol dependence. Approximately 63% of patients had a family history of alcohol problems (Table 27), and most (90%) patients smoked (Table 28). More than half (58%) of patients were under paid employment or self-employed (Table 29).
- Apart from alcohol dependence, 85% of patients in Cohort B had concurrent psychiatric, neurological, or other significant medical disorders (Table 34). The most common (≥10%) concurrent disorders (by preferred term) were: *hypertension* (40%), *hypercholestromia* (25%), *benign prostatic hyperplasia* (18% [sex-specific prevalence presented herewith]), *hepatic steatosis* (10%), and *type 2 diabetes mellitus* (10%). Approximately 21% of patients had medication discontinued prior to study inclusion (Table 35) and approximately 67% of patients had a concomitant medication continued after study inclusion (Table 36). Approximately 25% of patients started a concomitant medication at or after study inclusion (Table 37), and the most common ATC Level 3 group of medications prescribed were *antiinflammatory and antirheumatic products* (8%).

Exposure								
<ul style="list-style-type: none"> Exposure and adherence to IMP among patients in Cohort A are summarised in Tables 38 to 50. The mean number of days with IMP intake was 42 (Table 38), and the mean percentage of days with IMP intake was 54% (Table 39). The mean percentage of days that patients were adherent to IMP was 70% (Table 47), with approximately half of the patients (47%) being adherent to IMP on $\geq 80\%$ of the days. 								
Efficacy Results								
Cohort A:								
<ul style="list-style-type: none"> Alcohol consumption: <ul style="list-style-type: none"> The HDDs and TAC results for Cohort A are summarised below (FAS, MMRM): 								
	Baseline		Adjusted Change from Baseline			95% CI		
	N	Mean	Month	N	Mean	SE	Lower	Upper
Monthly Number of HDDs	301	24.1	1	301	-9.1	0.6	-10.2	-8.0
			2	274	-11.4	0.6	-12.6	-10.1
			3	262	-13.1	0.6	-14.4	-11.9
TAC (g/day)	301	111.2	1	301	-46.2	3.1	-52.3	-40.1
			2	274	-58.9	2.7	-64.2	-53.6
			3	262	-64.0	2.7	-69.4	-58.6
CI = confidence interval; SE = standard error Cross-reference: Tables 53 and 62 All results for alcohol consumption are summarised in Tables 51 to 59 (for HDDs), and 60 to 64 (for TAC).								
<ul style="list-style-type: none"> In Cohort A, there was a reduction in the mean number of HDDs over time. The mean number of HDDs decreased from 24 days/month at baseline to 15 days/month at Month 1, and to 11 days/month at Month 3 (FAS, OC; Table 51). The mean change from baseline in the number of HDDs at Month 3, based on the MMRM using FAS, was -13.1 days/month (95% CI: -14.4 to -11.9; $p < 0.0001$; Table 53). To support the results of the primary analysis, a sensitivity analysis of the primary endpoint was performed using an ANCOVA based on the FAS using LOCF. The mean change from baseline in the number of HDDs at Month 3 was -12.8 days/month (95% CI: -14.1 to -11.5; $p < 0.0001$; Table 56), and confirmed the improvement in the number of HDDs at Month 3 observed in the primary analysis. Subgroup analysis of HDDs by country was performed on an exploratory basis for Cohort A (Tables 57 to 59). In all countries, there was a reduction in the mean number of HDDs over time, and the mean change from baseline in the number of HDDs at Month 3, based on the MMRM using FAS, ranged from to -9.6 days/month (in the United Kingdom; 95% CI: -12.3 to -7.0; $p < 0.0001$) to -14.7 days/month (in Germany; 95% CI: -16.4 to -12.9; $p < 0.0001$) (Table 59). At baseline, the mean number of HDDs was highest in the United Kingdom (25 days/month) and lowest in Germany (23 days/month) (Table 57). In Cohort A, there was a reduction in the mean TAC over time. The mean number of TAC decreased from 111 g/day at baseline to 67 g/day at Month 1, and to 50 g/day at Month 3 (FAS, OC; Table 60). The mean change from baseline in TAC at Month 3, based on the MMRM using FAS, was -64.0 g/day (95% CI: -69.4 to -58.6; Table 62). Subgroup analyses of TAC by country was performed on an exploratory basis for Cohort A (Tables 63 and 64). In all countries, there was a reduction in the mean TAC over time, and the mean change from baseline in TAC at Month 3, based on FAS using OC, ranged from to -55.7 g/day (in Germany) to -68.9 g/day (in the United Kingdom) (Table 64). At baseline, the mean TAC was highest in the United Kingdom (135 g/day) and lowest in Germany (96 g/day) (Table 63). Response based on various drinking measures: <ul style="list-style-type: none"> The proportion of RSDRL responders was 55% (95% CI: 49.3 to 61.2; FAS, OC; Table 65) and the proportion of RLDRL responders was 44% (95% CI: 38.0 to 49.9; FAS, OC; Table 66). The proportion of R70 and R50 responders (based on TAC) was 37% (95% CI: 31.8 to 43.4; FAS, OC; Table 67) and 61% (95% CI: 55.0 to 66.8; FAS, OC; Table 68), respectively. The proportion of R0 responders (based on HDD) was 38% (95% CI: 32.1 to 43.8; FAS, OC; Table 69). 								

Efficacy Results (continued)• *Clinical global impression:*

- The results of the Clinical Global Impression (CGI) scale are summarised in Tables 70 to 74 for Cohort A. The mean CGI-S score decreased over time from 4.0 at baseline to 2.8 at Week 12 (FAS, OC; Table 70). The mean change from baseline in CGI-S score at Week 12, based on the MMRM using FAS, was -1.2 (95% CI: -1.3 to -1.1; Table 72).
- At all timepoints, the mean CGI-I score indicated improvements from baseline among patients in Cohort A (Table 73). At Week 12, the mean CGI-I score was 2.5 (95% CI: 2.3 to 2.6; Table 74).

• *Liver function:*

- Liver function was assessed by measuring levels of GGT, ALT, and AST, and the results are summarised in Tables 75 to 80 for Cohort A. The mean levels of GGT, ALT, and AST decreased over time from baseline to Week 12 (FAS, OC; Tables 75, 77, and 79). The geometric mean ratio at Week 12, based on the MMRM using FAS, was 0.87 for GGT (95% CI: 0.80 to 0.95; Table 76), 0.90 for ALT (95% CI: 0.84 to 0.97; Table 78), and 0.89 for AST (95% CI: 0.83 to 0.95; Table 80), respectively; a value of 1.0 reflects no change from baseline.

• *Health-related quality of life:*

- For patients in Cohort A that were living in France and the United Kingdom, health-related quality of life was assessed using the SF-36 (as a secondary efficacy measurement) and the AQLS (as an exploratory efficacy measurement). The results of the SF-36 are summarised in Tables 81 to 86, and the results of the AQLS are summarised in Tables 87 and 88.
- The SF-36 Mental Component and Physical Component scores each ranges from 0 to 100, with higher scores indicating better quality of life.¹ The mean change from baseline in SF-36 Mental Component score at Week 12 was 7.7 points (95% CI: 4.9 to 10.5; FAS, LOCF, ANCOVA; Table 85), and that for SF-36 Physical Component score was 2.2 points (95% CI: 0.6 to 3.9; FAS, LOCF, ANCOVA; Table 86). The minimal clinically important difference for the SF-36 Mental Component score is ≥ 3 ,² and therefore, the mean change from baseline of approximately 8 points indicates a highly clinically relevant improvement in mental health.
- The AQLS total score ranges from 0 to 102, with higher scores indicating worse quality of life.³ The mean change from baseline in AQLS total score at Week 12 was -17.6 points (FAS, OC; Table 88). The psychometric properties of the AQLS will be evaluated in a separate report.

Cohort B:• *Alcohol consumption:*

- The results for HDD and TAC are summarised in Tables 89 to 94 for Cohort B. In Cohort B, most of the reduction in HDDs appears to have occurred between the Screening Visit and the Inclusion Visit, where the mean number of HDDs was 5 days/month (Table 23). The mean change from the Inclusion Visit at Month 3 was 1.6 days/month (Table 91).
- In Cohort B, most of the reduction in TAC appears to have occurred between the Screening Visit and the Inclusion Visit, where the mean TAC was 31 g/day (Table 24). The mean change from the Inclusion Visit at Month 3 was 1.3 g/day (Table 94).

Safety Results**Death and Other SAEs in Patients Not Assigned to Either Cohorts A or B:**

- One patient died after screening but before the Inclusion Visit (see *Narratives of Death – Screening*). In addition, 3 patients had other SAEs after screening but before the Inclusion Visit (see *Narratives of Other Serious Adverse Events – Screening*). These 4 patients were not assigned to either Cohorts A or B and had not received any IMP.

Cohort A:

- *Adverse events:*
 - The adverse event incidence is summarised below:

	Cohort A	
	n	(%)
Number of patients	330	
Patients who died	1	(0.3)
Patients with serious adverse events (SAEs)	27	(8.2)
Patients with treatment-emergent adverse events (TEAEs)	211	(63.9)
Patients with AEs leading to withdrawal	21	(6.4)
Total number of SAEs		31
Total number of TEAEs		722
Total number of AEs leading to withdrawal		31

Cross-reference: Table 95

All adverse events in Cohort A are summarised in Tables 95 to 106, and listed in Listings 1 to 4.

- Fifty-two patients (17%) in Cohort A had pre-treatment adverse events (Table 96). Most pre-treatment adverse events occurred in 1 or 2 patients, except for *gamma-glutamyltransferase increased* (1%; n = 4), *nasopharyngitis* (1%; n = 4), *bronchitis* (1%; n = 3), *fall* (1%; n = 3), and *hypertension* (1%; n = 3), each of which occurred in 3 or more patients.
- Overall, 68% of patients in Cohort A had one or more TEAEs (Table 97). Most TEAEs occurred in <5% of patients (Table 98) and the TEAEs with an incidence $\geq 5\%$ were *nausea* (18%), *dizziness* (18%), *insomnia* (11%), *headache* (8%), and *vomiting* (6%) (Table 99). The proportion of patients who had TEAEs that were considered *related* to IMP was 53% (Table 101). The majority of the patients with *related* TEAEs had TEAEs that were either *mild* or *moderate* (Table 102).
- There was one death in Cohort A (Listing 3) – Patient S1054, a 44-year-old man, died of *hepatic cirrhosis* and *hepatic encephalopathy* on Day 94. For further details, refer to the individual narrative in *Narratives of Deaths – Cohort A*.
- In Cohort A, 22 patients (7%) reported 26 treatment-emergent SAEs (Table 103). None of the treatment-emergent SAEs in Cohort A occurred in >1 patient, except for *alcohol withdrawal syndrome*, *depressive symptom*, and *hepatic cirrhosis*, which occurred in 2 patients each (<1% each; Table 104). For further details, refer to the individual narratives in *Narratives of Other Serious Adverse Events – Cohort A*.
- The incidence of TEAEs leading to withdrawal from the study in Cohort A was 6% (Table 105). Most TEAEs leading to withdrawal from the study occurred in 1 or 2 patients, except for *nausea* (2%; n = 6) and *dizziness* (1%; n = 3), which occurred in 3 or more patients (Table 106). For further details, refer to the individual narratives in *Narratives of Adverse Events Leading to Withdrawal – Cohort A*.

Safety Results (continued)**• Clinical safety laboratory tests:**

- The laboratory values are summarised in Tables 107 to 113, and the changes therein from baseline are summarised in Tables 114 to 120. The reference ranges and potentially clinically significant (PCS) definitions are in Listing 10. As reference ranges for some tests are different for sex or age groups, the most restrictive upper and lower reference limits were used to evaluate the mean values.
- In Cohort A, the majority of the mean laboratory values were within the reference ranges at all scheduled visits, including the Screening Visit. However, for AST at baseline and for GGT at all scheduled visits (including baseline), the mean values were above the upper reference range (that is, >36 IU/L for AST and >95 IU/L for GGT). Elevated levels of AST and GGT are to be expected in patients with alcohol dependence and is an indication of liver function impairment. Importantly, decreases from baseline in mean levels of AST and GGT were observed over time (as well as for ALT; please see *Efficacy Results*). The mean changes from baseline for all other clinical safety laboratory tests were minimal and not clinically relevant. The incidences of post-baseline PCS laboratory values in Cohort A are summarised in Tables 121 to 127. The clinical safety laboratory tests with an incidence of post-baseline PCS values $\geq 5\%$ were PCS high glucose (20%), PCS high GGT (17%), and PCS high triglycerides (7%).
- The patients with PCS laboratory values are in Listing 11 and adverse events in patients with PCS laboratory values are in Listing 12. A total of 11 patients with PCS laboratory test values had 14 corresponding TEAEs: *gamma-glutamyltransferase increased* (n = 6), *blood glucose increased* (n = 3), *aspartate aminotransferase increased* (n = 2), *anaemia* (n = 2), and *liver function test abnormal* (n = 1). Of the 10 patients who had PCS laboratory test values reported as TEAEs, 4 patients also had PCS laboratory test values during the Screening Visit (Week -2).

• Vital signs:

- Vital signs and changes therein from the Inclusion Visit (baseline) are summarised in Tables 128 and 129, respectively. The reference ranges and PCS criteria are in Listing 10. The mean vital sign values were within the reference range at all-time points and the mean changes from baseline were minimal.
- The incidences of post-baseline PCS vital signs in Cohort A are summarised in Table 130. The individual PCS vital signs are in Listing 13 and adverse events in patients with PCS vital signs are in Listing 14. The incidence of post-baseline PCS vital signs was low. Three patients (1%) had PCS high systolic blood pressure (sitting) and 2 patients (<1%) had PCS high diastolic blood pressure (sitting) (Table 130). Of the patients who had PCS vital signs, 1 patient had *hypertension* reported as a non-serious adverse event (Listing 14).

• Weight:

- Weight and BMI and the changes therein from baseline are summarised in Tables 131 and 132, respectively. The PCS criteria are in Listing 10. At Week 12, patients in Cohort A had a mean weight loss of 0.4kg (Table 132) compared to baseline.
- The incidences of PCS weight changes are summarised in Table 133. The individual PCS weight changes are in Listing 15 and the adverse events in patients with PCS weight changes are in Listing 16. The incidence of PCS weight changes in Cohort A were generally low – 9 patients (3%) had PCS weight decrease and 6 patients (2%) had PCS weight increase. Of the patients that had PCS weight changes, 1 patient had *weight decreased* reported as a non-serious adverse event (Listing 16).

Safety Results (continued)**Cohort B:**• *Adverse events:*

- All adverse events in Cohort B are summarised in Tables 134 to 140, and listed in Listings 6 to 8. Overall, 33% of patients in Cohort B had one or more adverse events (Table 134). Most adverse events occurred in 1 or 2 patients, except for *nasopharyngitis*, which occurred in 4 patients (8%) (Table 135).
- There were no deaths in Cohort B and 1 patient had an SAE: *bronchospasm* (Table 139). The event did not lead to withdrawal from the study and the patient recovered from the event (Listing 7). For further details, refer to the individual narrative in *Narratives of Serious Adverse Events – Cohort B*.
- One patient in Cohort B withdrew due to an adverse event (*anxiety*) (Listing 8). Apart from this patient who withdrew due to an adverse event, no other patients in Cohort B withdrew from the study for any other reason (Listing 9). For further details, refer to the individual narratives in *Narratives of Adverse Events Leading to Withdrawal – Cohort B*.

Conclusions

- In the primary care setting, patients with alcohol dependence treated with as-needed use of 18mg nalmefene for 3 months in conjunction with continuous psychosocial support showed:
 - significantly reduced number of HDDs (with changes observed within the first month and continued improvements throughout the treatment period)
 - corresponding reduction in TAC
 - improvements in clinical global impression
 - improvements in liver enzymes (GGT, ALT, and AST)
 - substantial improvements in mental health (based on the SF-36 Mental Component score)
- Nalmefene was safe and well tolerated and no safety concerns were observed. The frequency and nature of adverse events reported were in accordance with previous knowledge of its safety. The majority of SAEs appeared to be related to the underlying disease.
- Patients who are not in need of additional pharmacotherapy, that is, those patients who were able to reduce their alcohol consumption during the screening period and therefore did not require nalmefene, could benefit from a brief intervention like approach provided in primary care.

Report Date

25 May 2016

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