

# Treating alcohol dependence with an abuse and misuse deterrent formulation of sodium oxybate: Results of a randomised, double-blind, placebo-controlled study

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RCT

## Abstract

Sodium oxybate (SMO) has been approved in Italy and Austria for the maintenance of abstinence in alcohol dependent (AD) patients. Although SMO is well tolerated in AD patients, cases of abuse and misuse have been reported outside the therapeutic setting. Here we report on a phase IIb double-blind, randomized, placebo-controlled trial for the maintenance of abstinence in AD patients with a new abuse and misuse deterrent formulation of SMO. A total of 509 AD patients were randomized to 12 weeks of placebo or one of four SMO doses (0.75, 1.25, 1.75 or 2.25 g t.i.d.) followed by a one-week medication-free period. The primary endpoint was the percentage of days abstinent (PDA) at end of treatment. An unexpectedly high placebo response (mean 73%, median 92%) was observed. This probably compromised the demonstration of efficacy in the PDA, but several secondary endpoints showed statistically significant improvements. A post-hoc subgroup analysis based on baseline severity showed no improvements in the mild group, but statistically significant improvements in the severe group: PDA: mean difference +15%, Cohen's  $d = 0.42$ ; abstinence: risk difference +18%, risk ratio = 2.22. No safety concerns were reported. Although the primary endpoint was not significant in the overall population, several secondary endpoints were significant in the intent-to-treat population and post-hoc results showed that treatment with SMO was associated with a significant improvement in severe AD patients which is consistent with previous findings. New trials are warranted that take baseline severity into consideration.

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## 1. Introduction

Alcohol dependence (AD) is the most severe form of alcohol use disorders with a prevalence of 7.7% in the United States of America (World Health Organization, 2018) and of 3.4% in the European Union (Rehm et al., 2015). About two-thirds of the overall alcohol-attributable mortality in the European Union is due to AD and similar estimates have been given for other areas of the world (Rehm and Shield, 2012). There is strong evidence that alcohol-related harm is determined by the volume of alcohol consumed and the drinking pattern (Rehm et al., 2010; Rehm and Shield, 2012). The volume of alcohol consumption has been categorized in different Drinking Risk Levels (DRL) by the WHO (World Health Organization, 2000). Alcohol dependent subjects with a Very High DRL are considered to be the most severely affected population of alcohol users (Rehm et al., 2018).

One of the AD treatment objectives is the achievement of stable abstinence by prevention of relapse after detoxification (European Medicines Agency 2010). Currently, disulfiram, acamprosate and naltrexone are regis-

tered in the United States of America and in Europe for the treatment of AD, and nalmefene is registered by the European Medicines Agency (EMA) for reduced alcohol consumption in AD patients with a High or Very High DRL. Although effective on the group level, effects sizes are limited, and many AD patients fail to respond to these medications (European Medicines Agency 2010; Litten et al., 2013; van den Brink et al., 2018). Therefore, additional pharmacological treatments are needed.

Sodium oxybate (SMO) as an oral solution (Alcover®) has been approved in Italy and Austria for the treatment of alcohol withdrawal syndrome and the maintenance of abstinence since 1991 and 1999, respectively (van den Brink et al., 2018). SMO is the sodium salt of  $\gamma$ -hydroxybutyric acid (GHB), a short-chain fatty acid that occurs naturally in the mammalian brain. GHB binds with low affinity to GABA subtype B (GABA<sub>B</sub>) receptors and with high affinity to GHB-specific receptors (Keating, 2014). Given that the pharmacological profile of GHB has similarities to that of alcohol, one proposed mechanism is that SMO has an alcohol-

mimicking effect (i.e. substitutes for alcohol) in the brain (Keating, 2014). SMO 50 mg/kg/day oral solution showed evidence of efficacy compared to placebo and naltrexone in the maintenance of abstinence in AD patients in a series of open label and blinded randomized controlled trials (RCTs) and was positively evaluated in a Cochrane review (Caputo et al., 2007, 2003; Gallimberti et al., 1992; Leone et al., 2010). However, studies were generally small and almost all of them used only one fixed dose of SMO.

SMO oral solution in the treatment of AD has been well-tolerated both in clinical trials and in therapeutic use in Italy and Austria (Addolorato et al., 2020). However, cases of abuse, dependence and criminal misuse (e.g. attempt to drug another person) have been reported when (illicit) GHB is not controlled and not used as a therapeutic agent (Addolorato et al., 2009; Németh et al., 2010). Since these risks cannot be neglected, a new oral granules in sachet formulation of SMO was developed that is bioequivalent to Alcover and aims to minimize the risk of abuse, misuse, and particularly criminal use of SMO. The granules present a low SMO load and are flavoured (apple), effervescent, partly insoluble with floating cores. An important and difficult to ingest quantity of granules is needed to reach SMO toxic doses and granules are noticeable when put in a drink preventing the risk of criminal misuse (additional information with pictures is provided in supplementary material).

Here, we present the results from a phase IIb double-blind placebo-controlled RCT in 509 AD patients, which aimed to investigate the efficacy and safety of this new SMO formulation in the maintenance of abstinence over a dose range from 0.75 to 2.25 g t.i.d.. Secondary objectives were 1) to assess possible SMO craving or withdrawal, abuse, or misuse, 2) to define the optimal dose or dose range of SMO, and 3) to assess the effect of SMO on other clinically relevant secondary efficacy endpoints.

## 2. Experimental procedures

### 2.1. Patients

This double-blind, randomized, placebo-controlled, outpatient trial included patients from 56 centers in Austria, Czech Republic, France, Germany, Italy, Poland, Slovakia, Spain, and Sweden. Eligible patients were assessed based on structured interview, physical examination, measurement of vital signs and laboratory parameters. Men and women aged 18 to 75 years with a BMI between 18.5 and 30 kg/m<sup>2</sup>, who met  $\geq 4$  DSM-IV-R criteria for AD, who confirmed  $\geq 7$  drinking days including  $\geq 2$  heavy drinking days (HDDs) in the last 14 days before screening and who, in the judgement of the investigator were motivated to abstain from alcohol, were included. A HDD was defined as  $\geq 5$  drinks per day in males and  $\geq 4$  drinks per day in females.

Further, patients had to be abstinent for 3-14 days with or without formal in- or outpatient detoxification before randomization and potential detoxification supporting medication had to be stopped  $\geq 24$  h before randomization.

Patients with severe hepatic or renal impairment or with a history of drug abuse or dependence (except nicotine and caffeine) or with current DSM-IV axis 1 psychiatric disorder requiring medical treatment or with moderate to severe depression or anxiety were not included in the study.

The protocol, the patient information, consent form, and other relevant study documentation were approved by 27 independent

Ethics Committees (ECs) for each study site before initiation of the trial. Central ECs were involved for sites in France, Germany, Poland, Sweden, and Spain (one EC per country) whereas study documentation was approved by local ECs in the remaining countries (several ECs per country). This clinical study was registered in the EU Clinical Trials Register (EudraCT 2011-000575-14) and conducted in accordance with the ethical principles of the Declaration of Helsinki and with the Good Clinical Practices. Written informed consent was obtained from all patients.

### 2.2. Randomization and blinding

Following the screening visit, patients meeting the inclusion criteria were randomly assigned to 1 of 5 treatment groups according to a randomized block design in a ratio of 1:1:1:1:1 to each of the 4 SMO dose groups or placebo, in a blind manner and with blocks of five patients. The randomization lists were generated by an independent biostatistician. Central randomization was applied using Interactive Voice Response System and/or Interactive Web Response System.

Sponsor, investigators, and patients were blind to treatment assignment. Blinding was achieved by administration of blinded 1-week treatment kits containing sachets of either SMO or placebo. SMO and placebo granules were identical in appearance and taste.

### 2.3. Study procedures

#### 2.3.1. Intervention

The study consisted of an up to two-week screening period, a 12-week double-blind treatment phase with one of four SMO doses (0.75, 1.25, 1.75, and 2.25 g t.i.d.) or placebo, abrupt discontinuation of the study medication and a one-week follow-up period to evaluate any treatment discontinuation effects. Dose selection was based on the Alcover® summary product characteristics and the results of previous clinical studies: the 1.25 g t.i.d. and the 1.75 g t.i.d. doses were expected to be safe and effective to maintain alcohol abstinence (see supplementary material for additional information).

Patients were instructed to take one sachet three times a day (morning, noon, and evening) in fasted conditions with approximately 200 ml of water.

All patients took part in Brief Behavioral Compliance Enhancement Treatment (BBCET; Johnson et al., 2003) starting at randomization and subsequently at all scheduled visits. BBCET aimed at maintaining abstinence from alcohol and enhancing compliance with the study medication. At each visit, patients were carefully informed about the risk of concomitant use of alcohol with study medication, especially about the risk of sedation.

#### 2.3.2. Assessments

Study visits in the double-blind treatment phase were planned for every week for the first 4 weeks and every 2 weeks of the remaining 8 weeks of this phase. At screening, patients reported their daily drinking over the previous 14 days. At subsequent visits, they reported the number of standard daily drinks since the previous visit. The assessment of alcohol consumption was based on patient self-report, using the Timeline Follow Back calendar method (Sobell and Sobell, 1992) (see supplementary material for the conversion of standard drinks to grams of pure alcohol). Return to any drinking was considered as a relapse. Alcohol dependence severity at baseline was measured with the Alcohol Dependence Scale (ADS; Skinner and Horn, 1984).

#### 2.3.2.1. Primary outcome

The primary efficacy endpoint was the Percentage of Days Abstinent (PDA) during the double-blind treatment phase. PDA was calculated

as the ratio expressed as a percentage of the number of days with no alcohol intake to the total number of days of the double-blind treatment phase (84 days).

#### 2.3.2.2. Secondary outcomes

Key secondary outcome measures for the treatment phase were abstinence rate, the number of Heavy Drinking Days (HDDs) during the 12-week treatment period, the percentage of subjects with no HDD during the 12-week treatment period, the change from baseline in the number of HDDs at Month 3 (week 9 to 12), the change from baseline in the total alcohol consumption (TAC) at Month 3 (week 9 to 12), the time to relapse since the start of treatment and the responder rate at end of treatment. The abstinence rate was defined as the proportion of patients with a continuous abstinence throughout the 12-week treatment period. The responder rate measured the proportion of patients with a mean TAC during Month 3 lower than 40 g/day (Gallimberti et al., 1992). The abstinence rate, the number of HDD, the percentage of subjects with no HDDs and the time to relapse since the end of treatment were also analyzed for the one-week follow-up period. PDA was also calculated during the last four weeks of the study period, i.e., including the one-week follow-up period (week 10 to 13).

Alanine aminotransferase (ALT), aspartate aminotransferase (ASAT), mean corpuscular volume (MCV),  $\gamma$ -glutamyltransferase (GGT), and the percentage of carbohydrate-deficient transferrin (%CDT) were determined at each visit.

Craving for alcohol was assessed with the self-report Obsessive Compulsive Drinking Scale (OCDS; Anton et al., 1995) as well as with its compulsive and resistance/impairment subscale scores. The compulsive subscale score corresponds to items 7 to 14 of the OCDS scale and the resistance/impairment subscale score refers to items 5, 6, 7, 8, 12 and 14.

Safety assessments consisted in the evaluation of Adverse Events (AEs), clinical laboratory parameters, physical examinations, vital signs, electrocardiogram, concomitant medications, the Columbia-suicide severity rating scale, and an ad-hoc study medication craving scale.

For additional information on assessed endpoints, see supplementary material.

## 2.4. Statistical analysis

The sample size calculation was based on a group difference between placebo and SMO of 12% in PDA with a standard deviation of 25%. Using the assumed variability and a two-sided  $\alpha = 0.0125$ , 99 patients in each treatment group would provide a power of 80%. The  $\alpha = 0.0125$  was chosen to address the multiplicity issue of 4 separate dose comparisons of SMO against placebo. No statistical testing between specific SMO dose groups was performed. Analyses of secondary endpoints were not adjusted for multiplicity.

Two datasets were pre-specified in the study protocol. The *Safety Population* set was predefined as all randomized subjects who received at least one dose of study medication and was used for all safety endpoints. The *Intent-To-Treat* set was predefined as all randomized subjects who received at least one dose of study medication and have at least one post-baseline measurement and was used for efficacy endpoints.

The predefined analysis of PDA was based on an analysis of variance (ANOVA) model with factors for treatment, site, and baseline ADS score. In addition, an unadjusted treatment effect and a treatment effect adjusted only for site were computed in sensitivity analyses. Linear regression models were used to investigate the relationship between the response in PDA and the patients' bodyweight in each treatment group. Abstinence rate and responder rate were analyzed using relative risk and risk difference as effect indicators with confidence intervals. Continuous secondary

outcomes were analyzed with similar models as for the primary outcome.

Results from preclinical studies suggest a dose-response following an inverted U-shape and the need for an adjustment of the dose in mg/kg based on the level of alcohol consumption at baseline (Colombo and Gessa, 2000). Therefore, the dose-response relationship on PDA based on patients' bodyweight was post-hoc investigated with quadratic regression models. SMO fixed doses received t.i.d. by enrolled patients were converted in mg/kg/day doses using patients' body weight. Quadratic regression models were applied in the ITT population and separately in the patient population with High or Very High DRL at baseline.

A subgroup analysis based on population severity at baseline was performed because recent studies suggest that the placebo response in double-blind RCTs is lower and pharmacological treatment effect sizes are larger in AD patients with a High or Very High DRL (>60 g alcohol/day for men and >40 g alcohol/day for women; at baseline; Rehm et al., 2018) and with less than 14 consecutive days of abstinence before randomization ('severe population') than in the complement population with Low or Medium DRL at baseline or more than 14 consecutive abstinent days before randomization ('mild population') (Gual et al., 2013; Gueorguieva et al., 2011, 2012; Mann et al., 2016; van den Brink et al., 2013, 2014, 2018). Since these populations were identified in some other studies when the current study was already completed, post-hoc analyses were performed to investigate SMO efficacy in each of these populations separately. These analyses were conducted in accordance with the European Medicines Agency guideline on exploratory subgroup analyses in confirmatory trials (European Medicines Agency, 2019). The interaction between treatment groups and population severity on PDA was tested with a generalized linear model with the following terms: PDA = treatment + population + treatment\*population. In this analysis, treatment and population were categorical variables with five (placebo, 0.75 g, 1.25 g, 1.75 g, 2.25 g t.i.d.) and two (severe, mild) categories, respectively. Efficacy was analyzed for primary and key secondary endpoints. Each SMO dose-group as well as the pooled SMO group were compared to placebo. To illustrate the evolution of the response of the pooled SMO group and of the placebo group over the study period, PDA was analyzed by week in each subgroup with descriptive statistics.

For the double-blind treatment phase, and in accordance with the protocol, dropout and missing data were considered as a relapse to alcohol for PDA and abstinence rate. No imputation was used for the follow-up data. Additional information on the imputation methods is provided in supplementary material.

All AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1.

For additional information on the above statistical analyses, see supplementary materials. The principal statistical software used was SAS®, Version 9.4.

## 3. Results

### 3.1. Study sample

From October 2012 to March 2014, 647 patients were screened of whom 511 were randomized, two did not receive the allocated drug and thus 509 were included in the Safety Population (Fig. 1). Because they had no post-baseline efficacy measurements, 13 patients in the Safety Population were excluded from the ITT Population. The efficacy analyses were conducted using the ITT Population, which included a total of 496 patients: 99 patients in the placebo group and 99, 99, 99, and 100 patients in the SMO 0.75, 1.25, 1.75, and 2.25 g groups, respectively. The number of patients enrolled per country is provided in Table S1.



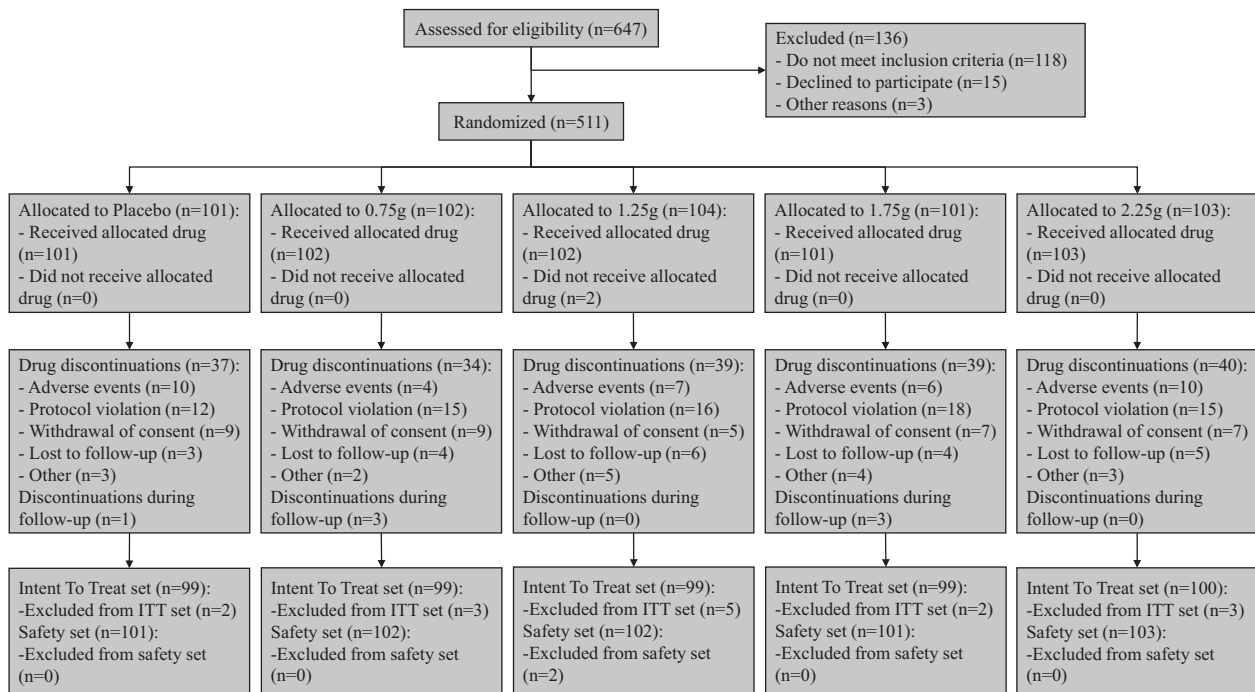


Fig. 1 Patient flowchart.

Table 1 Demographics and baseline clinical characteristics: mean (sd).

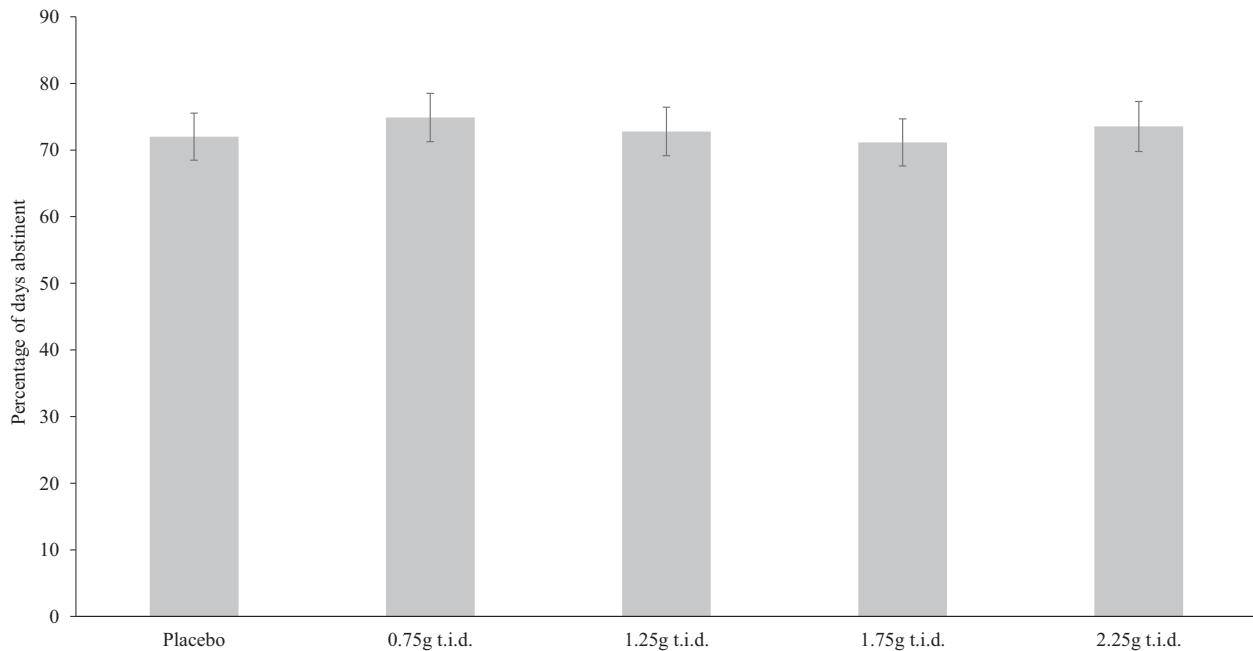
	Placebo	0.75 g	1.25 g	1.75 g	2.25 g
N	99	99	99	99	100
Age	48.3 (11.2)	47.1 (11.9)	47.4 (10.4)	48.1 (11.6)	47.7 (11.2)
Gender: females n (%)	32 (32.3)	22 (22.2)	24 (24.2)	22 (22.2)	24 (24.0)
Weight	75.3 (12.4)	75.1 (14.9)	76.9 (12.3)	78.9 (13.8)	75.6 (13.6)
BMI	25.3 (3.3)	24.4 (3.6)	25.3 (3.2)	25.9 (3.3)	24.8 (3.1)
Age of onset of dependence	34.5 (11.7)	35.6 (11.0)	34.8 (11.3)	34.2 (12.9)	34.5 (9.9)
TAC (g alcohol/day)	65.5 (37.0)	54.6 (26.9)	62.8 (38.5)	58.7 (33.6)	60.4 (35.7)
HDD (days/month)	19.8 (7.5)	16.2 (7.6)	17.4 (7.8)	17.4 (7.4)	17.7 (7.9)
GGT	99.6 (150.0)	52.5 (66.8)	83.4 (109.5)	104.7 (265.3)	92.2 (185.2)
ALAT	38.6 (31.9)	31.9 (23.4)	33.5 (22.7)	35.9 (24.7)	33.5 (26.2)
ASAT	37.9 (33.3)	29.7 (25.3)	31.2 (21.4)	32.7 (24.5)	31.6 (21.6)
MCV	100.2 (6.7)	99.1 (6.7)	99.7 (6.3)	98.4 (5.8)	99.8 (6.6)
%CDT	1.6 (1.4)	1.8 (1.8)	1.8 (2.0)	1.9 (2.3)	2.1 (2.3)
DRL					
L n (%)	18 (18.2%)	25 (25.3%)	24 (24.2%)	20 (20.2%)	24 (24.0%)
M n (%)	39 (39.4%)	54 (54.5%)	42 (42.4%)	50 (50.5%)	43 (43%)
H n (%)	21 (21.2%)	9 (9.1%)	14 (14.1%)	15 (15.2%)	15 (15%)
VH n (%)	20 (20.2%)	10 (10.1%)	18 (18.2%)	14 (14.1%)	18 (18%)
Unknown n (%)	1 (1.0%)	1 (1.0%)	1 (1.0%)		
ADS	17.3 (6.9)	15.3 (6.0)	16.3 (7.2)	15.7 (6.9)	15.2 (5.4)
OCDS	15.5 (10.2)	12.8 (9.0)	12.6 (10.0)	12.9 (9.3)	13.9 (8.9)

TAC: total alcohol consumption; HDD: heavy drinking days; GGT:  $\gamma$ -glutamyltransferase; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; MCV: mean corpuscular volume; CDT: carbohydrate-deficient transferrin; DRL: Drinking Risk Level; L: Low; M: Medium; H: High; VH: Very High; ADS: Alcohol Dependence Scale; OCDS: Obsessive Compulsive Drinking Scale.

A total of 189 of the 511 randomized patients (37.0%) did not complete the 12-week treatment phase because of protocol violation (76 patients), consent withdrawal (37 patients), AEs (37 patients), lost to follow-up (22 patients), investigator decision (11 patients), other (4 patients), and study terminated by the sponsor (2 patients). The main pro-

tol violations in the ITT population were use of prohibited concomitant medication ( $n = 20$ ), exclusion criteria met ( $n = 18$ ), compliance  $<80\%$  ( $n = 16$ ). Non-completion rates were similar in the five treatment arms.

There were no clinically relevant differences in baseline demographic or clinical characteristics between the five



**Fig. 2** Mean percentage of days abstinent during the treatment period in ITT population. Bars indicate standard errors.

groups (Table 1). A total of 339 patients (68.4%) had a Low or Medium DRL at baseline and were included in the mild severity population and 154 (31.0%) had a High or Very High DRL and were classified as the severe population. Alcohol consumption at baseline was not reported for 3 patients (0.6%) and their DRL was considered unknown (Table 1). No clinically relevant treatment group differences were identified in baseline characteristics of patients in the severe or in the mild severity population (see Tables S2 and S3).

### 3.2. Efficacy in primary and secondary endpoints

In the ITT population, the mean differences in the PDA adjusted for site and ADS between SMO 0.75, 1.25, 1.75, 2.25 g t.i.d. and placebo at the end of the treatment phase were not significant (Table 2; Figure 2). Similar results were obtained for the unadjusted treatment effect and the treatment effect adjusted for site only (Table S4). It should be noted, however, that the PDA placebo response was unexpectedly high (mean 72.5%, median 91.7%).

Importantly, several SMO doses (notably 1.75 g t.i.d.) showed statistical significant effects compared with placebo in secondary endpoints in the ITT population: 1) during the treatment period significant group differences were observed in the number of HDDs, the end-of-treatment OCDS subscale scores for compulsive and resistance, and the %CDT at end-of-treatment, and 2) during the one-week follow-up significant group differences were observed in abstinence rate, time-to-relapse, the percentage of subjects with no HDDs and the number of HDDs (Table 2). More detailed results of primary and secondary endpoints are presented in supplementary Tables S4–7.

### 3.3. Dose-response relation

Dose-response analyses showed that treatment response in terms of PDA was negatively correlated with bodyweight only in the SMO 0.75 g t.i.d. group ( $p = 0.011$ ;  $R^2 = 0.25$ ), indicating a higher SMO response in patients with lower bodyweights in this dose group. Interestingly, when the SMO fixed doses t.i.d. were converted in mg/kg/day, an inverted U-shape dose-response relationship was identified. Quadratic regression models were statistically significant in the ITT-population ( $p < 0.001$ ) and in the severe population ( $p < 0.05$ ). The peak of the inverted U-shape was reached at the SMO dose of 18 mg/kg/day in the ITT population (composed for 68% of Low or Medium DRL patients) and 60 mg/kg/day in patients with a High or Very High DRL at baseline (inverted U-shape curve is presented in Figure S1).

### 3.4. Efficacy in severe and mild populations

A significant interaction ( $p = 0.001$ ) was detected between treatment groups and population severity on PDA, indicating that the treatment effect was significantly dependent on population severity. In the severe population ( $N = 154$ ), pooled SMO doses showed statistically significant higher PDA during the 12-week treatment period compared to placebo: treatment difference +15.0%,  $p = 0.022$ , Cohen's  $d = 0.42$ . In this severe subpopulation SMO treatment was also associated with significantly better key secondary outcomes compared to placebo: PDA last four weeks (treatment difference +24.3%,  $p = 0.003$ , Cohen's  $d = 0.55$ ), abstinence rate (risk difference +18.1%,  $p = 0.04$ , risk ratio = 2.22), responder rate (risk difference +22.9%,  $p = 0.027$ , risk ratio = 1.60), change from baseline at Month 3 in TAC (treatment difference −21.0 g/day,  $p = 0.027$ , Cohen's  $d = 0.41$ ),

**Table 2** Summary and Analysis of primary and secondary endpoints in ITT Population.

Difference to placebo	SMO 0.75 g t.i.d.	SMO 1.25 g t.i.d.	SMO 1.75 g t.i.d.	SMO 2.25 g t.i.d.
<i>Percentage of Days Abstinent (PDA) 12-week treatment period</i>				
Adj mean difference	2.87	0.78	−0.86	1.53
95%CI	−6.49, 12.24	−8.66, 10.22	−10.16, 8.43	−7.83, 10.88
p-value	0.547	0.871	0.856	0.749
<i>Number of HDD - treatment period</i>				
Adj mean difference	−1.46	−0.18	−2.00	0.64
95%CI	−3.28, 0.36	−2.02, 1.65	−3.81, −0.19	−1.18, 2.46
p-value	0.116	0.845	0.030	0.488
<i>OCDS - Compulsive Subscale Score - End of treatment</i>				
Adj mean difference	−0.6	−1.6	−2.2	0.0
95%CI	−2.1, 1.0	−4.2, 0.9	−3.9, −0.5	−1.8, 1.7
p-value	0.471	0.207	0.013	0.965
<i>OCDS - Resistance/Impairment Subscale Score - End of treatment</i>				
Adj mean difference	−0.3	−1.9	−1.7	0.0
95%CI	−1.6, 0.9	−4.0, 0.1	−3.1, −0.3	−1.4, 1.4
p-value	0.598	0.068	0.016	0.995
<i>%CDT - End of treatment</i>				
Adj mean difference	−0.26	−0.62	−0.49	−0.51
95%CI	−0.78, 0.25	−1.14, −0.10	−1.01, 0.03	−1.04, 0.01
p-value	0.313	0.019	0.066	0.056
<i>Abstinence rate - one week follow-up</i>				
Risk difference	19.7%	15.9%	17.6%	11.1%
95%CI	4.2 ; 35.2	−0.1 ; 31.9	1.6 ; 33.7	−5.3 ; 27.6
p-value	0.013	0.052	0.031	0.185
Risk ratio	1.33	1.26	1.29	1.18
95%CI	1.05, 1.68	0.99, 1.61	1.02, 1.65	0.919, 1.53
p-value	0.018	0.060	0.038	0.192
<i>Number of HDD - one week follow-up</i>				
Adj mean difference	−0.50	−0.26	−0.55	−0.46
95%CI	−0.93, −0.07	−0.69, 0.18	−0.98, −0.12	−0.88, −0.03
p-value	0.022	0.244	0.013	0.035
<i>Percentage of subjects with no HDD - one week follow-up</i>				
Odds ratio	4.10	2.20	4.87	2.30
95% CI	1.25, 13.44	0.81, 5.99	1.31, 18.19	0.84, 6.28
p-value	0.020	0.123	0.018	0.105
<i>Time to relapse - one week follow-up</i>				
Adj Hazard ratio	0.39	0.61	0.48	0.43
95%CI	0.18, 0.80	0.31, 1.21	0.24, 0.96	0.23, 0.82
p-value	0.011	0.157	0.038	0.010

ITT = intent-to-treat; t.i.d = 3 times a day. Adj = Adjusted for site and ADS; OCDS - Compulsive Subscale Score: items 7 to 14 of the OCDS scale; OCDS - Resistance/Impairment Subscale Score: items 5,6,7,8, 12 and 14 of the OCDS scale.

change from baseline at Month 3 in the number of HDD (treatment difference −5 HDD/month,  $p = 0.015$ , Cohen's  $d = 0.45$ ). In contrast, pooled SMO doses in the mild population showed (statistically significant) deteriorations compared to placebo (Fig. 3 and supplementary Tables S8-10), which explains that in the overall analysis a null effect was found (Table 2). In the severe population, the treatment difference between SMO and placebo was higher in the PDA computed over the last four weeks than in the PDA over the 12-week treatment period (Fig. 3). Several SMO dosages showed a statistically significant superiority compared with placebo in primary and secondary endpoints in the severe population (supplementary Table S9). The higher SMO treatment effect in the severe population is mainly explained by

a significantly lower placebo response in the severe compared to the mild population (mean PDA of 54% versus 87%,  $p < 0.0001$ ; Fig. 3).

### 3.5. Safety and tolerability

The most frequently reported treatment-emergent adverse events (TEAEs) were headache, dizziness, nasopharyngitis, fatigue, and vertigo, with dizziness, fatigue and vertigo being more prevalent in patients on higher SMO doses (Table 3). The number of patients with TEAEs leading to permanent discontinuation of study medication ranged from

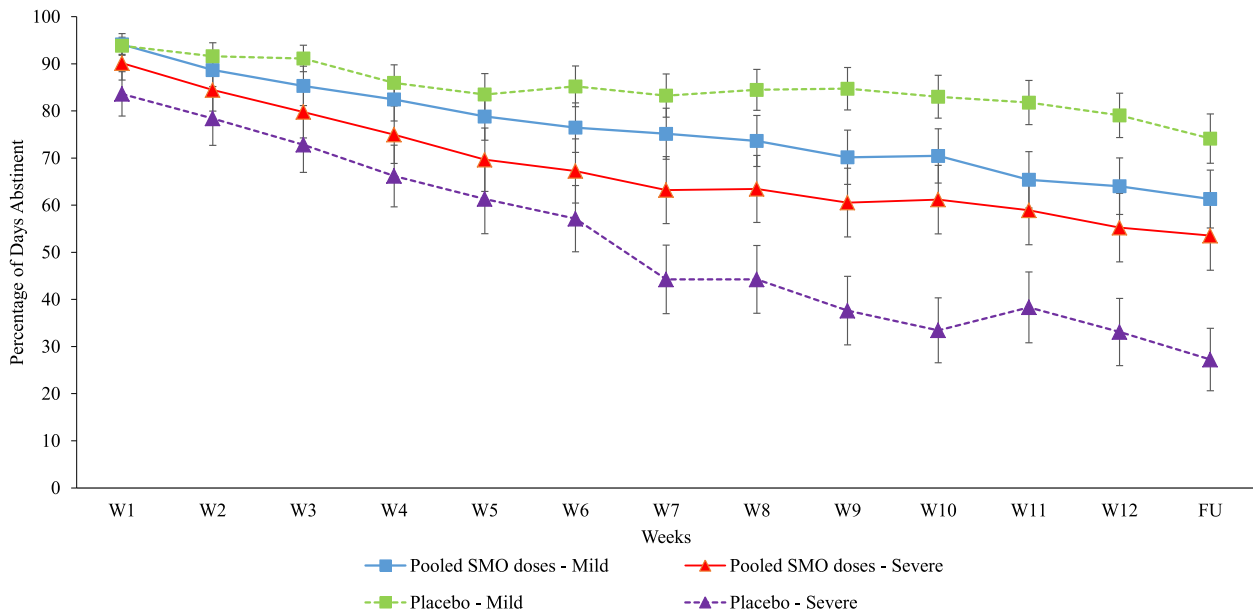


Fig. 3 Mean Percentage of Days Abstinent per week in severe and mild population. Bars indicate standard errors.

Table 3 Treatment Emergent Adverse Events – Safety Population.

	Placebo N = 101	0.75 g tid N = 102	1.25 g tid N = 102	1.75 g tid N = 101	2.25 g tid N = 103
Any TEAE	75 (74.3)	73 (71.6)	73 (71.6)	87 (86.1)	81 (78.6)
TEAEs ( $\geq 5\%$ )					
Headache	23 (22.8)	24 (23.5)	15 (14.7)	18 (17.8)	19 (18.4)
Dizziness	7 (6.9)	7 (6.9)	16 (15.7)	25 (24.8)	28 (27.2)
Nasopharyngitis	13 (12.9)	8 (7.8)	13 (12.7)	16 (15.8)	10 (9.7)
Fatigue	6 (5.9)	6 (5.9)	9 (8.8)	11 (10.9)	13 (12.6)
Vertigo	3 (3.0)	4 (3.9)	9 (8.8)	17 (16.8)	12 (11.7)
Somnolence	8 (7.9)	8 (7.8)	0	10 (9.9)	11 (10.7)
Insomnia	7 (6.9)	12 (11.8)	6 (5.9)	8 (7.9)	4 (3.9)
Nausea	3 (3.0)	4 (3.9)	7 (6.9)	8 (7.9)	10 (9.7)
Diarrhea	9 (8.9)	6 (5.9)	6 (5.9)	5 (5.0)	3 (2.9)
Anxiety	7 (6.9)	6 (5.9)	5 (4.9)	3 (3.0)	7 (6.8)
TEAEs leading to dropout	10 (9.9)	4 (3.9)	8 (7.8)	7 (6.9)	10 (9.7)
SAEs related to study medication	1 (1.0)	0	1 (1.0)	0	2 (1.9)

Data are numbers of patients (%). SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

four to ten patients in the different SMO groups compared with 10 patients in the placebo group.

No deaths were reported. The number of patients in the SMO groups who experienced non-fatal treatment-emergent serious adverse events (SAEs) ranged from zero to two patients and was numerically similar to patients in the placebo group (one patient). A total of 4 patients experienced 5 treatment emergent SAEs that were considered by the investigator to be related to study medication: joint dislocation (placebo), toxicity to various agents (SMO 2.25 g t.i.d.), epilepsy (SMO 1.25 g t.i.d.), loss of consciousness (SMO 2.25 g t.i.d.), and discomfort (2.25 g t.i.d.). Loss of consciousness and discomfort were reported in a 45-year-old female patient treated with SMO 2.25 g t.i.d. who relapsed (15 drinks) on the day of the event.

Based on the Columbia-Suicide Severity Rating Scale, three (0.73%) patients had suicidal behavior and/or ideation at some moment in time during the period of active treatment with SMO compared with three patients (3%) in the placebo group.

There were 1746 cumulative days of concomitant exposure to alcohol and SMO. No respiratory depression and no cases of abuse or diversion were reported.

Regarding craving for study medication, the mean score of all study groups was about two points out of the maximum of ten points at week 12. Craving for the medication increased in week 13 (follow-up without treatment) with a mean score of 5.7 points (SD = 5.5) in the placebo group, 5.7 points (SD = 5.1) in the 0.75 g t.i.d. group, 3.0 points (SD = 2.7) in the 1.25 g t.i.d. group, 3.3 points (SD = 0.6) in



the 1.75 g t.i.d. group, and of 4 points (SD = 2.7) in 2.25 g t.i.d. group.

#### 4. Discussion

Sodium oxybate (SMO) oral solution has previously shown efficacy in the maintenance of abstinence in a series of small RCTs and observational studies (Caputo et al., 2007, 2003; Gallimberti et al., 1992; Leone et al., 2010; Marenmani et al., 2001). The current Phase IIb double-blind RCT with a new misuse and abuse deterrent SMO formulation did not show evidence of SMO efficacy in the primary endpoint, the PDA. The observed placebo response (mean PDA 73%; median 92%) was much higher than anticipated (20–40% expected based on prior studies) which may have compromised the demonstration of efficacy. It is recognized that studies often fail when the placebo response is unexpectedly high and that the placebo response in AD studies cannot be reliably predicted (European Medicines Agency 2007; Litten et al., 2013). Several secondary endpoints were statistically significant in favor of SMO, especially during the follow-up period. However, effect sizes were small and of limited clinical relevance during the treatment period and clinically relevant only during the follow-up period with risk differences in the abstinence rate of +17.6% and +19.7% in favor of the 1.75 g t.i.d. and 0.75 g t.i.d. groups, respectively.

These results are somewhat in contrast with previous trials testing SMO efficacy in AD. This is not uncommon in this therapeutic domain where most of the approvals of medications were based on a mix of negative and positive studies with some degree of uncertainty regarding the true effect (European Medicines Agency 2010). Moreover, treatment effects were generally negatively correlated with the placebo response in the studies (Litten et al., 2013). It is, therefore, important to determine the moderators of the treatment effect as well as the target population in which these medications are effective. In this context, post-hoc analyses on dose-response and population severity at baseline were conducted in accordance with the methodology recommended by the EMA for the investigation of subgroups in confirmatory trials (European Medicines Agency, 2019).

An inverted U-shape dose-response relation influenced by the level of alcohol consumption at baseline and body weight has been identified: the more alcohol consumed at baseline, the higher the SMO dose in mg/kg to be administered. The pharmacology of SMO with its ability to mimic some effects of alcohol in the brain supports an adjustment of the SMO dose based on the patient's alcohol consumption at baseline. Ethanol moiety is present in the structure of GHB and they share various pharmacological and neurochemical characteristics (Gallimberti et al., 1992). Its role as a substitute for alcohol is supported by evidence of SMO efficacy in the prevention and the treatment of alcohol withdrawal in several trials and in a meta-analysis (Addolorato et al., 1999; Caputo et al., 2014; Gallimberti et al., 1989; Leone et al., 2010; Moncini et al., 2000; Nava et al., 2007). A drug discrimination study conducted in rats also showed that substitution for ethanol was an inverted U-shape function of SMO dose in mg/kg (Colombo et al., 1995; Colombo and Gessa, 2000). Further-

more, in healthy volunteers, ethanol and SMO at 1/12 to 1/17 of the alcohol dose in mg/kg produced similar subjective, cognitive, physiological, and reinforcing effects in three studies (Abanades et al., 2007; Johnson and Griffiths, 2013; Oliveto et al., 2010). Given these data, some researchers suggest that SMO can be conceptualized as a substitution treatment for alcohol in AD patients (Chick and Nutt, 2012).

In addition to the identification of a dose-response relationship, population severity was mentioned in the literature as an effect modifier predicting both placebo response and treatment effect of several approved medications in the treatment of AD only after the current Phase IIb trial was completed. In these studies, the subgroups (severe vs. mild) were defined by baseline DRL and the drinking pattern during two weeks pre-randomization (Gual et al., 2013; Gueorguieva et al., 2011, 2012; Mann et al., 2013, 2016; Reynaud et al., 2017; van den Brink et al., 2013, 2014, 2018; European Medicines Agency 2012). Given these recent findings, the effect of population severity on SMO efficacy was investigated in the current study. The significant treatment-by-population severity interaction ( $p = 0.001$ ) on PDA indicated that the treatment effect was dependent on population severity. In the severe population, the placebo response was lower and SMO showed statistically significant and clinically relevant results in PDA and in most secondary endpoints such as abstinence rate. In contrast, no efficacy was shown in the current study in the mild severity population where the placebo response was very high (mean PDA 87%). In a mildly severe population, the psychosocial support, the impact of the placebo administration on neurotransmitters and the strict clinical supervision may be sufficient to improve the outcomes in many patients and this may explain this very high placebo response (Krol et al., 2020).

The study design and the fact that 68% of the enrolled population in the current study were AD patients with mild severity at baseline may explain the overall high placebo response and the negative results in the primary endpoint. In four recent European RCTs, 31% to 67% of the randomised AD patients had mild severity at baseline (Reynaud et al., 2017; van den Brink et al., 2013, 2014). Possible explanations for the differences in the proportion of mild-severity patients across studies include potential differences in inclusion/exclusion criteria and/or concerns related to potential risks of giving placebo to severely ill patients (Krol et al., 2020).

The adverse event profile was as expected from previously published data with the oral solution (Addolorato et al., 2020) and reflects the pharmacological profile of SMO. The incidence of TEAEs leading to dropout and of SAEs related to study medication were comparable between all groups. The two SAEs reported in one patient (loss of consciousness and discomfort) were associated with concomitant administration of a high SMO dose (130 mg/kg/day) and relapse to heavy drinking (15 drinks/day). Therefore, it is recommended to suspend or discontinue the treatment with SMO in case of relapse to heavy drinking. All treatment groups showed a mild craving for study medication that was on the lower end of the scale. No cases of SMO abuse were reported. Overall, SMO was well-tolerated, and no safety concerns were reported.

## Limitations

Drop-out rates during the treatment period were between 33.3% and 38.8% across the five treatment groups and were consistent with those commonly observed in AD trials and those from RCTs that were used to establish efficacy of approved compounds in the treatment of AD (European Medicines Agency, 2012; Nice, 2011). However, drop-outs were considered as drinking days/treatment failures in the analysis of the PDA and the abstinence rate.

Several secondary endpoints showed a statistically significant effect of SMO during the follow-up period suggesting a better sustainability of treatment for SMO than placebo. However, the one-week follow-up duration is too short and studies with a longer (treatment free) follow-up are needed to establish whether stable treatment results with SMO can be achieved (European Medicines Agency 2010).

Efficacy results in the severe population and the inverted U-shape dose-response derive from post-hoc analyses in subpopulations. Due to issues of multiple testing and jeopardized randomization, results from post-hoc subgroup analyses should be interpreted with caution (Higgins et al., 2020). In the current study and although subgroup analyses were not based on randomized comparisons, no clinically relevant treatment group differences in baseline characteristics were identified between patients in the severe and the mild severity population. Regarding multiplicity, EMA does not recommend any adjustment of the nominal significance level and considers that the credibility and interpretation of *a posteriori* subgroup findings depend on the replication and the plausibility of the results (European Medicines Agency, 2019). In this respect, population severity in our study is based on the existing literature and this factor distinguishes heavy drinkers without “spontaneous improvement” prior to treatment initiation (severe) from other patients (mild). Spontaneous improvement prior to randomization is a recognized predictor of higher placebo response in other therapeutic areas such as depression, anxiety, angina, dyslipidemia, hypertension (Doering et al., 2014; Sonawalla and Rosenbaum, 2002; US Food and Drug Administration, 2019). In addition, there is growing evidence that population severity is a predictor of placebo response and an effect modifier for several pharmacotherapies in the treatment of AD. In a review analyzing treatment effects of SMO and of other approved medications for the treatment of AD, acamprosate, naltrexone and nalmefene all failed to show clinically relevant effects versus placebo in the mild population, whereas they were all modestly effective in the severe population (van den Brink et al., 2018). In the current study, the treatment-by-population severity interaction was highly significant. SMO did not show evidence of efficacy in the mild population whereas it did show significant improvement in the severe population in both PDA (mean difference +15%, Cohen's  $d = 0.42$ ) and abstinence rate (risk difference +18.1%, risk ratio 2.22). Similar results have been reported in a double-blind placebo-controlled RCT ( $N = 82$ ) and in two open label naltrexone-controlled RCTs ( $N = 35$  and  $N = 55$ ) with SMO conducted in severe populations where SMO (50 mg/kg/day) was significantly superior to placebo in PDA (mean difference of +18% and Cohen's  $d = 1.18$ ) and in abstinence rate (risk difference

of +22% and risk ratio of 5.35) and to naltrexone in abstinence rate (risk difference of +31.4% and 34.1%; risk ratio of 1.89 and 6.80) (Gallimberti et al., 1992; van den Brink et al., 2018). In contrast, SMO showed evidence of efficacy with only small effect sizes in three RCTs with treatment duration of 6 to 12 months conducted in mild populations (van den Brink et al., 2018). However since the placebo response in RCTs for AD was dependent on treatment duration with higher relapse rates in studies with a longer treatment duration (Anton et al., 2005, 1999; Baltieri et al., 2008; Baltieri and Andrade, 2003; Chick et al., 2000; Kiefer et al., 2003; Pelc et al., 1997; Volpicelli et al., 1997), these positive findings of SMO efficacy in mild populations may be explained by a longer treatment duration in these RCTs compared to the treatment duration in the current study.

In conclusion, the primary endpoint was not significant in the overall population, but several secondary endpoints were significant in the intent-to-treat population and post-hoc results showed that treatment with SMO was associated with a statistically significant and clinically relevant improvement in severe AD patients which is consistent with previous findings. Data suggest an adjustment of SMO dose based on patient's alcohol consumption at baseline and body weight, a finding supported pharmacologically and by preclinical and external clinical data. However, since these significant and clinically relevant results were derived from post-hoc subgroup analysis, additional data from other relevant trials are needed in this population. To focus on the high drinking subgroup holds relevance especially in relation to alcohol related disabilities and mortality rates. We are aware that also other subgroupings, e.g. according to genetic, neurobiological and other clinical features, might be important as predictors for the SMO treatment effect. They represent decisive factors for course, therapy and outcome (Lesch et al., 2020).

## Conflict of Interest Disclosures

JG is employed by D&A Pharma, Paris, France. RP and QR were employed by D&A Pharma when the data were analysed. None of the other authors received financial support for the current work. GA, HJA, PB, AB, Antoni Gual, OL, IM, PP, BS, HW were investigators for the study. WvdB received financial support related to the current work from Lundbeck, Novartis, Bioproject, and Kinov Therapeutics. WvdB received financial support not related to the current work from Recordati, Mundipharma, Angelini, Opiant, Indivior, and Takeda. GA and OL served as consultants for D&A Pharma, and were paid for their consulting services. GA has received lecture fees from D&A Pharma. RS received financial compensation from D&A Pharma for consultations. IM served as board member for Angelini, Camurus, CT Sanremo, D&A Pharma, Gilead, Indivior, Lundbeck, Molteni, MSD, Mundipharma. HJA reported being member of advisory boards or DSMB for Bioproject, CV Sciences, and Ethypharm, and has received sponsorship to attend scientific meetings, speaker honoraria or consultancy fees from Bioproject, D&A Pharma, Ethypharm, Kinov Pharmaceuticals and Lundbeck. He is also member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initia-

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## Sponsor

Sponsor name: D&A Pharma; Sponsor Protocol Number: SMO032/10/03.

Clinical trial registration: Randomized, multi-center, double-blind, placebo-controlled study of the safety and efficacy of 4 dose regimens of SMO.IR, an oral solid formulation of sodium oxybate, in the maintenance of alcohol abstinence in recently abstinent alcohol-dependent patients; registered in EU Clinical Trials Register ([https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract\\_number:2011-000575-14](https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-000575-14)); EudraCT number: 2011-000575-14

## Role of the funding source

The sponsor was involved in the study design, data collection, data analysis, and interpretation of the data. JG is employed by D&A Pharma. RP and QR were employed by D&A Pharma when the data were analysed. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

## Author Contributions

All authors were involved in the design of the study and/or data analysis and/or interpretation. JG designed the *post hoc* analyses. OL was the signatory investigator for the study. JG wrote the manuscript and all authors contributed to and have approved the final manuscript.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.euroneuro.2021.06.003](https://doi.org/10.1016/j.euroneuro.2021.06.003).

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