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Sodium oxybate for the treatment of alcohol dependence

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Our greatest glory is not in never falling, but in rising every time we fall.

– Confucius –

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CHAPTER 1

General introduction

INTRODUCTION

This thesis reports the results of a clinical development and research project with the aim to expand access to sodium oxybate (SMO) for the treatment of alcohol dependence (AD). According to the last revision of the International Classification of Diseases (ICD-11), AD is a disorder of regulation of alcohol use arising from repeated or continuous use of alcohol (World Health Organization, 2019). AD is responsible for substantial morbidity and mortality (Rehm et al., 2015, 2012, 2010). The goals of AD treatment include reduced drinking and achievement of sustained abstinence. AD patients targeting achievement of sustained abstinence are often first detoxified, if necessary treated for the alcohol withdrawal syndrome (AWS), and then follow a maintenance of abstinence programme. Unfortunately, many AD patients fail to respond to currently available medications for the maintenance of abstinence (acamprosate, naltrexone, disulfiram) and none is also effective in the treatment of AWS (European Medicines Agency, 2010a; van den Brink et al., 2018). Therefore, additional pharmacological treatments are needed, probably including SMO.

SMO is the sodium salt of γ-hydroxybutyric acid (GHB). SMO has an alcohol-mimicking effect on the central nervous system and has shown efficacy in the treatment of AWS and in the maintenance of abstinence in AD patients in a series of open label and blinded randomized controlled trials (RCTs) (Addolorato et al., 1999; Caputo et al., 2014, 2007, 2003; Gallimberti et al., 1992, 1989; Nava et al., 2007, 2006) and was positively evaluated for these indications in a Cochrane review some years ago (Leone et al., 2010). SMO as an oral solution (Alcover® - Figure 1) has been approved in Italy and Austria for the treatment of AWS and for the maintenance of abstinence in AD patients since 1991 and 1999, respectively (van den Brink et al., 2018).

However, studies in the maintenance of abstinence were generally small and almost all of them used a fixed dose of SMO. Moreover, these studies did not investigate the sustainability of the SMO effect after treatment discontinuation and unexplained heterogeneity of the SMO treatment effect was identified across studies. Regarding tolerability and safety, SMO oral solution in the treatment of AD was well-tolerated both in clinical trials and in standard clinical use in Italy and Austria (Addolorato et al., 2020). However, cases of abuse and diversion of (illicit) GHB have been reported (Addolorato et al., 2009; Németh et al., 2010). Therefore, to expand access to SMO in the treatment of AD in countries other than Austria and Italy, further developments and studies were needed notably using an abuse/diversion deterrent SMO formulation.

Figure 1. Alcover®-sirup approved in Austria

This journey started in 2000 with the aim to further support the efficacy and safety of SMO in the treatment of AD and to improve its benefit-risk ratio in this indication in view of expanding its access in other countries. In total, 30+ international researchers/clinicians, 70+ investigators, senior statisticians, two pharmaceutical companies, and 5+ clinical research organizations were involved in this clinical development and research trajectory.

This introduction describes the AD condition, the available treatment options for AD apart from SMO, and the still existing medical need. It then summarizes the mechanism of action of SMO and discusses the RCTs that investigated the efficacy and the safety of SMO in the treatment of AWS and in the maintenance of abstinence in AD patients. The introduction ends with an overview of the aims and an outline of this thesis.

ALCOHOL DEPENDENCE

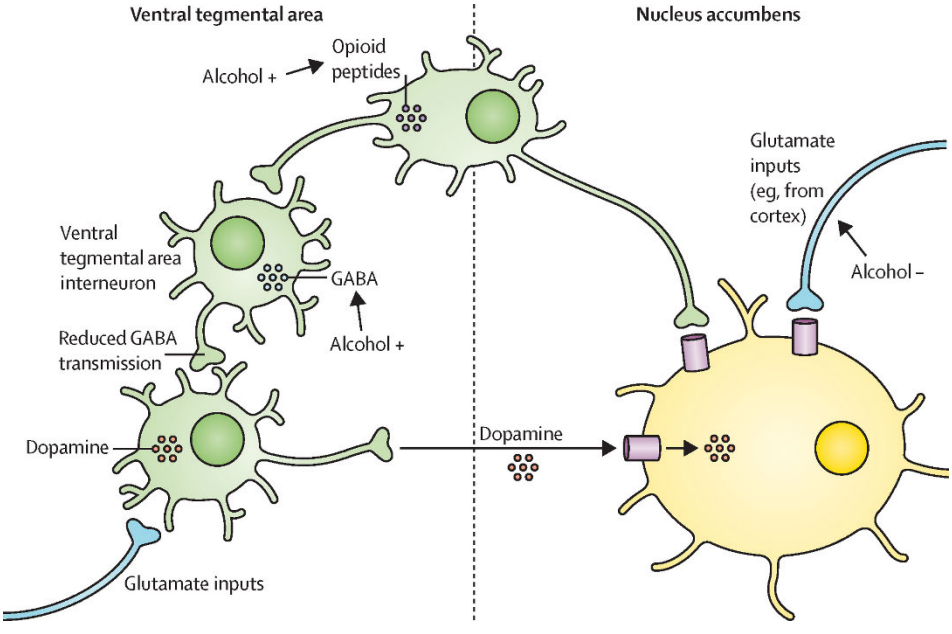
Alcohol dependence (AD) is generally defined as a chronic (relapsing) disease with genetic and environmental factors influencing its development and manifestations (European Medicines Agency, 2010a). According to the ICD-11, AD is characterized by impaired control over drinking, sensation of urge to use alcohol (craving), continued use of alcohol despite adverse consequences, and distortions in thinking, most notably denial, a higher priority given to alcohol use than to other activities and obligations, and finally AWS and increased tolerance (World Health Organization, 2019). In contrast with ICD-11, AD is no longer referenced in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). DSM–5 integrates two DSM–IV disorders, alcohol abuse and AD, into a single disorder called alcohol use disorder (AUD) with mild,

moderate, and severe sub-classifications based on the number of AUD-criteria that are present: mild AUD with 2-3 of the 11 AUD-criteria; moderate AUD with 4-5 of the 11 AUD-criteria; and severe with ≥6 of the 11 AUD-criteria (National Institute on Alcohol Abuse and Alcoholism, 2021). Research has shown that DSM-5 mild AUD and moderate-severe AUD are largely equivalent to DSM-IV alcohol abuse and alcohol dependence, respectively (and especially so in clinical samples) (Goldstein et al., 2015). Nevertheless, the European Medicines Agency (EMA) currently considers that alcohol abuse is not an appropriate target indication and that the developments of new medications for alcohol addiction for the European Union (EU) should focus on the treatment of AD (European Medicines Agency, 2010a).

Current research suggests several pathways involved in the development and persistence of AD (Figure 2), including the opioid and dopamine systems, which seem to cause alcohol craving and relapse due to positive reinforcing effects of alcohol consumption, especially in earlier stages of the disease. A second pathway involves several components of the gamma-aminobutyric acid (GABA)/glutamate system, which is involved in the development of alcohol craving and relapse due to a hyperglutamatergic state. A further pathway seems to be a hypodopaminergic state, especially after chronic alcohol intake, which is associated with a state of dysphoria that promotes resumption of alcohol intake (European Medicines Agency, 2010a).

AD affects 3.4% of the general population aged 18-64 years in the EU (Rehm et al., 2015). AD is associated with high alcohol consumption, and thus leads to altered metabolic pathways as a consequence of ethanol oxidation in the liver hepatocytes resulting in an increase in fatty acids leading to steatosis (Aithal and Grove, 2015). Ethanol's metabolite acetaldehyde can cause deoxyribonucleic acid (DNA) damage and block DNA synthesis and repair, whilst both ethanol and acetaldehyde can disrupt DNA methylation. Ethanol can also induce inflammation and oxidative stress leading to lipid peroxidation and further DNA damage (Rumgay et al., 2021). Therefore, AD is associated with acute and chronic health consequences, most notably various cancers, liver cirrhosis, pancreatitis, cardiovascular diseases, intentional and unintentional injuries and AWS (Rehm et al., 2010; World Health Organization, 2018). AWS is a clinically significant cluster of symptoms, behaviours and/or physiological features, varying in severity and duration, that occurs upon abrupt cessation or reduction of alcohol use in individuals who have developed AD or have used alcohol for a prolonged period and/or in large amounts (World Health Organization, 2019). AD is also highly disabling (World Health Organization, 2018) and the disabling effects can manifest themselves in absenteeism from work, failure to fulfil one's social roles, and other interpersonal problems and functional problems in daily life (Ormel, 1994; Samokhvalov et al., 2010).

Figure 2. Effects of alcohol on selected neurotransmitter systems from Connor et al., 2016



The ventral tegmental area is located close to the midline on the floor of the midbrain and contributes to pleasure and reward through projections to the nucleus accumbens, which has an important role in the cognitive processing of pleasure, reward, and reinforcement learning. Alcohol is thought to stimulate endogenous opioid peptides and GABA receptor activity (marked by "Alcohol+") in the ventral tegmental area, and inhibit release of the excitatory neurotransmitter glutamate from nerve terminals that act on neurons in the nucleus accumbens (marked by "Alcohol–"). These actions enhance dopaminergic transmission. Repeated exposure to alcohol over time leads to adaption to these effects.

As a consequence, about 12% of the overall mortality in the EU is due to AD (Rehm et al., 2012) and subjects with alcohol use disorders have an average life expectancy of 47–65 years and die 12–28 years earlier than people in the general population (Schwarzinger et al., 2017; Westman et al., 2015). This reduced but broad range of life expectancy can be explained by the age of onset of AD and the volume of alcohol consumed. There is strong evidence that alcohol-related harm is mainly determined by the volume of alcohol consumed (Rehm et al., 2012, 2010). Therefore, the volume of alcohol consumption has been categorized in different Drinking Risk Levels (DRL) by the World Health Organization (WHO) (World Health Organization, 2000). The WHO DRLs were defined based on 16 cohort studies which showed increased mortality/morbidity risk at each of the sex-specific levels of alcohol consumption (Table 1) (World Health Organization, 2000).

Table 1. WHO Drinking Risk Levels

Drinking level category	Average daily consumption of ethanol (grams per day)	
	Male	Female
Low risk	>0 to ≤40	>0 to ≤20
Moderate risk	>40 to ≤60	>20 to ≤40
High risk	>60 to ≤100	>40 to ≤60
Very high risk	>100	>60

Source: World Health Organization, 2000

AVAILABLE TREATMENT OPTIONS APART FROM SMO AND MEDICAL NEED

The goals of AD treatment include the achievement of sustained abstinence, reduction in frequency and severity of relapse, reduction in the total amount of drinking, and improvement in health and psychosocial functioning. AD patients targeting achievement of sustained abstinence are detoxified and then follow a maintenance of abstinence programme.

During the detoxification phase, patients with severe withdrawal symptoms are usually treated for 5 to 7 days in an in-patient or out-patient setting often with benzodiazepines to reduce central nervous system irritability, fluids to prevent dehydration, thiamine (vitamin B1) to prevent Wernicke/Korsakov and if necessary further medications such as anticonvulsants and antipsychotic agents to prevent or treat withdrawal seizures and delirium (Bahji et al., 2022; European Medicines Agency, 2010a). Efficacy of benzodiazepines in the management of alcohol withdrawal, in the prevention of complications such as seizures and delirium, and in ameliorating the severity of alcohol withdrawal has been clearly shown (Bahji et al., 2022). Clomethiazole is also approved and used in the treatment of AWS in some countries, such as Austria and Germany (Mann et al., 2017; Nimmerrichter et al., 2002).

For the maintenance of abstinence phase, together with the traditionally offered variety of psychosocial interventions designed to optimise the chances of achieving long-term abstinence from alcohol, several pharmacotherapeutic agents are used to optimise long-term abstinence (Mann et al., 2004). Approved medicines in the maintenance of alcohol abstinence in the United States of America (USA) and in Europe include acamprosate, naltrexone and disulfiram. In addition, nalmefene and baclofen have been registered for the reduction of alcohol consumption in AD patients with a High or Very High DRL in the EU

and in France, respectively. However, these medicines only show modest efficacy with mixed-results and with many patients not responding to these treatments (European Medicines Agency, 2010a; Litten et al., 2012; van den Brink et al., 2018). Disulfiram and naltrexone are contraindicated in patients with hepatic impairment and acamprosate in patients with renal impairment (van den Brink et al., 2018). Furthermore, a majority of people with AD in the EU receive no treatment for their AD (Rehm et al., 2012; Tuithof et al., 2016) and the probability to receive medication to prevent relapse is even smaller.

Given the burden caused by AD and the need for additional interventions, the WHO considers the development of new medicines for the treatment of AD as one of the 24 priority medicines for Europe and the World. Priority medicines represent a list of high-burden diseases for which the development of new medicines is a priority due to the presence of an unmet medical need (Kaplan et al., 2013). Similarly, in 2016, members of the Medications Development Team of the US National Institute of Alcohol Abuse and Alcoholism (NIAAA) recognized the treatment of AD as an important unmet medical need (Litten et al., 2016).

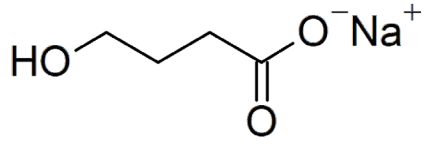
SMO IN THE TREATMENT OF ALCOHOL DEPENDENCE

Mechanism of action of SMO

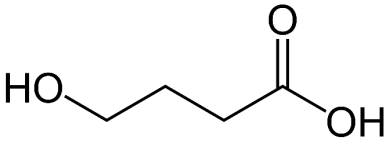
SMO is the sodium salt of GHB (Figure 3), which is naturally present in human and animal tissues as a neurotransmitter. GHB is found in the human brain and binds to both high-affinity (GHB-receptor) binding sites and low-affinity ($GABA_B$ receptor) binding sites.

Figure 3. Chemical structures of SMO and GHB

Sodium oxybate



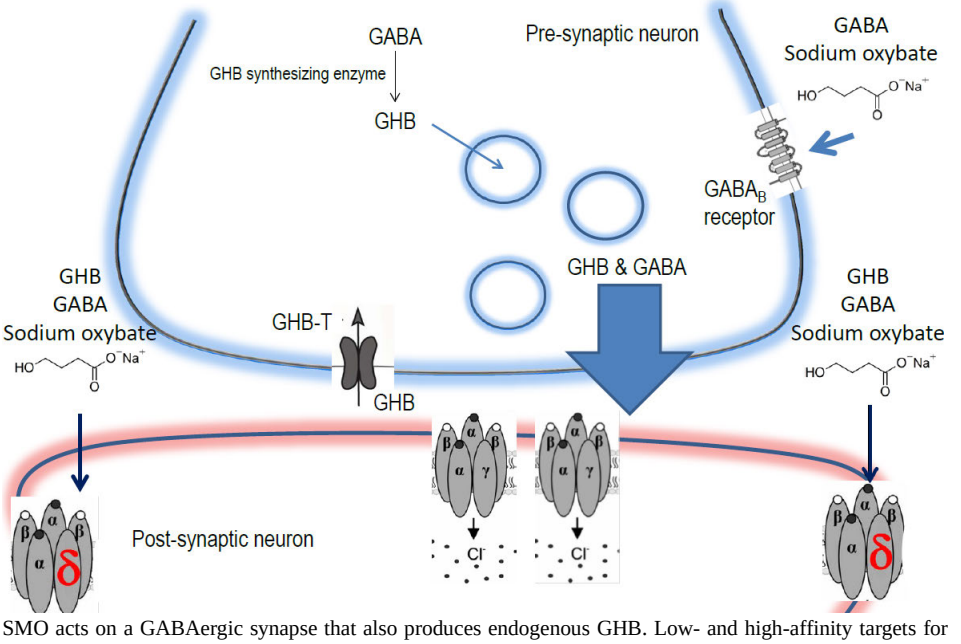
GHB



The best-established target for GHB is the $GABA_B$ receptor (Figure 4), at which GHB displays low affinity and is a partial agonist. However, endogenous GHB levels are generally low and $GABA_B$ receptor activation most likely only occurs after exogenous GHB/SMO intake, e.g., after recreational or therapeutic drug administration. Under such circumstances, $GABA_B$ receptors account for some of the reported in vivo effects of SMO, including sedation (Bay et al., 2014).

Endogenous GHB also acts through high-affinity extra-synaptic binding sites popularly referred to as GHB receptors, which are clearly distinct from $GABA_B$ receptors (Figure 4). Extra-synaptic $GABA_A$ receptors that contain α4/δ-subunits are the most responsive GHB sites (Absalom et al., 2012; Connelly et al., 2013). Extra-synaptic $GABA_A$ receptors are responsible for a tonic inhibition of GABA release and, importantly, they are also the primary targets for ethanol (Spanagel, 2009). It is thus suggested that SMO produces an alcohol mimetic euphoric action, at least in part, through these sites (van den Brink et al., 2018).

Figure 4. The mode of action of SMO according to Bay et al. (2014)



SMO acts on a GABAergic synapse that also produces endogenous GHB. Low- and high-affinity targets for GHB are activated by either exogenous SMO or synaptically released GHB. The metabotropic GABAB receptors (low-affinity) are activated after exogenous GHB/SMO intake. The GHB high-affinity sites are extra-synaptically located, part of which may be represented by α4β1δ GABAA receptors. GHB-T refers to GABA transporter molecules.

Thus, on the neurochemical level both endogenous and exogenous GHB have a dual action on GHB and $GABA_B$ receptors. At low doses, SMO seems to have alcohol-mimetic euphoric effects that may be explained by a predominant effect of SMO action on GHB receptors. In this respect, SMO showed efficacy and is approved in the maintenance of abstinence in AD patient at a posology of 50mg/kg/day (2.5 to 4.5g/day) divided into three administrations. At medium to high SMO doses, a sedative effect has been observed which may be due to a predominant effect of SMO action on $GABA_B$ (Skala et al., 2014). Thanks to its properties to increase deep sleep and increase the amount of time spent asleep at night, SMO showed efficacy at doses from 4.5 to 9g/night (divided into two administrations) in the treatment of narcolepsy with cataplexy. SMO improved the symptoms of narcolepsy by reducing the number of sleeping periods during the day. SMO has thus been approved for this indication at the above posology in the USA and in the EU in 2002 and 2005, respectively (European Medicines Agency, 2021, 2006). Tolerance can develop to the GHB sedative-hypnotic effects but has not been reported at SMO therapeutic doses (Addolorato et al., 2019; Kamal, 2016). GHB physical dependence and withdrawal syndrome were reported, almost exclusively in illicit GHB users with very high daily doses (range from 10g to 312g/day, mean 59g/day), markedly exceeding the therapeutic dose regimen of pharmaceutical SMO (Kamal, 2016).

Efficacy of SMO in the treatment of AWS

For ethical reasons (potentially life-threatening condition) and since effective treatments are available, almost all recent trials in the treatment of AWS are benzodiazepine-controlled. To have assay sensitivity, equivalence or non-inferiority benzodiazepine-controlled trials should include patient populations with moderate or severe AWS at baseline as these patients do not improve without effective treatment (Adinoff, 1994; Krupitsky et al., 2007; Lyon et al., 2011). In this context, the efficacy of oral SMO in the treatment of acute AWS has been evaluated in 7 published studies (670 patients) with five RCTs including patients with moderate to severe AWS (Addolorato et al., 1999; Caputo et al., 2014; Gallimberti et al., 1989; Nava et al., 2007; Nimmerrichter et al., 2002) and two non-controlled studies (Korninger et al., 2003; Moncini et al., 2000).

RCTs on SMO efficacy in the treatment of AWS

In the double-blind, placebo-controlled pilot RCT conducted by Gallimberti et al. (1989) in 23 AD patients with moderate AWS at baseline, SMO (50mg/kg/day) was significantly more effective than placebo. In contrast with the placebo group, nearly all withdrawal symptoms disappeared within 2 to 7 hours after treatment initiation in the SMO group. (Gallimberti et al., 1989).

In the phase III, international (4 EU countries), double-blind, double-dummy, oxazepam-controlled equivalence GATE 1 RCT in 127 AD patients with moderate AWS at baseline, SMO (≈75mg/kg/day) was equivalent to oxazepam (210 mg/day) in the reduction of AWS symptoms from baseline to end of treatment (day 10). The intensity of AWS symptoms was close to the minimum score (no symptom of withdrawal at all) in both groups at end of treatment (Caputo et al., 2014; European Medicines Agency, 2020).

In the open, diazepam controlled RCT conducted by Nava et al. (2007) in 42 AD patients with severe AWS, SMO (50 mg/kg/day) was significantly more effective than diazepam (0.5 mg/kg/day) in reducing withdrawal symptoms at each time point (Day 7, 14, and 21). The intensity of AWS symptoms at end of treatment was close to the minimum score (no symptom of withdrawal at all) in the SMO group. No medical complications were observed (Nava et al., 2007).

In the diazepam controlled, single-blind RCT including 60 AD patients with moderate AWS severity at baseline, Addolorato et al. (1999) showed that SMO (50mg/kg/day) and diazepam (0.5-0.75 mg/kg/day) were equally effective in the treatment of AWS at the end of the 10-day treatment period. The intensity of AWS symptoms at end of treatment was close to the minimum score (no symptom of withdrawal at all) in both groups (Addolorato et al., 1999).

In a double-blind, double-dummy, clomethiazole-controlled RCT in 98 AD patients with moderately severe AWS at baseline, SMO 50mg/kg/day and SMO 100mg/kg/day were as effective as clomethiazole (1000 mg/day) in reducing withdrawal symptoms. The intensity of withdrawal symptoms at end of treatment was close to the minimum score (no symptom of withdrawal at all) in all groups (Nimmerrichter et al., 2002).

Meta-analyses of RCTs on SMO efficacy in the treatment of AWS

In a meta-analysis performed by the Cochrane Collaboration, SMO 50mg/kg/day was significantly more effective than placebo and clomethiazole for withdrawal symptoms (Leone et al., 2010). In a network meta-analysis comparing the efficacy and safety of different medications for alcohol withdrawal, SMO was significantly more effective than placebo in the reduction of the alcohol withdrawal symptoms (Cohen's d -1.80) (Bahji et al., 2022).

Non-controlled studies on SMO effect in the treatment of AWS

SMO also showed an effect in the management of AWS in 299 patients who were admitted to hospital for reasons unrelated to their AD in a non-controlled study in an hospital setting. The effect of SMO (50mg/kg/day) to ameliorate or suppress the AWS was judged to be excellent in 57%, good in 34%, fair in 18%, and insufficient in 3% of the patients (Korninger et al., 2003). In another uncontrolled study, SMO (50–150 mg/kg/day) showed an effect in the treatment of 22 AD

patients with a diagnosis of severe AWS, with symptoms of hallucinations in 8 patients and seizures in 3 patients. Nearly all withdrawal signs and symptoms (including seizures and hallucinations) disappeared after 4 days, and total remission of AWS was observed after 10 days (Moncini et al., 2000).

Conclusion on SMO efficacy in the treatment of AWS

In conclusion, SMO efficacy in the treatment of AWS is supported by data from five RCTs, including a phase III trial (Caputo et al., 2014). Results showed that SMO is (at least) as effective as a benzodiazepine (diazepam, oxazepam) and clomethiazole and superior to placebo in treating uncomplicated alcohol withdrawal symptoms. As detailed below, SMO can also be used for the maintenance of abstinence program, avoiding a switch of medication. The SMO effect in patients with complications such as seizures and delirium tremens has been evaluated only in a very small uncontrolled study.

Efficacy of SMO in the maintenance of abstinence

The efficacy of oral SMO in the maintenance of alcohol abstinence was initially evaluated in 10 studies: five RCTs with treatment durations from 3 to 12 months and five uncontrolled studies. However, a confirmatory (phase III) trial was still missing. For confirmatory trials directed at maintenance of abstinence in AD patients, EMA recommends to conduct placebo-controlled RCTs with a treatment duration of 3 to 6 months followed by a medication-free period, for a total study duration of 12 to 15 months (European Medicines Agency, 2010a, 2010b). The recommended primary endpoint is the ‘abstinence rate’ which is the proportion of patients with continuous abstinence (no relapse to any drinking) over the treatment period. The Percentage of Days Abstinent (PDA) has also been used in certain studies and it measures the ratio between the number of days with no alcohol use and the planned number of treatment days for each patient.

RCTs on SMO efficacy in the maintenance of abstinence

As illustrated in Table 2, five RCTs compared SMO efficacy and safety with placebo (Di Bello et al., 1995; Gallimberti et al., 1992), naltrexone (Caputo et al., 2007, 2003; Nava et al., 2006) or disulfiram (Nava et al., 2006).

Table 2. SMO effect in the maintenance of abstinence in published RCTs

RCTs	N	Comparator(s)	Endpoint	Results in (co-)primary endpoints	
				Treatment difference/Excess rate	p-value
Gallimberti et al., 1992	82	Placebo	PDA TAC AR	+17.5% -4.6 drinks/day +24.8%	<0.001 <0.01 0.02
Caputo et al., 2003	35	NTX	AR	+31.4%	0.02
Caputo et al., 2007	55	NTX NTX+SMO	AR	+34.1% vs NTX -32.2% vs NTX+SMO	0.04 0.03
Nava et al., 2006	55	NTX DSF	ACS	-1.9 vs NTX -1.4 vs DSF	<0.001 <0.001
			AR	+16% vs NTX +25% vs DSF	0.08[a]
Di Bello et al., 1995	17	Placebo	ACS AR	-2.0 +16.6%	<0.05 0.5

NTX: naltrexone; SMO: sodium oxybate; DSF: disulfiram; PDA: percentage of days abstinent; TAC : total alcohol consumption; AR: abstinence rate;
[a] single p value based on chi square test; treatment duration of 3 months in all studies except Nava (12 months) and Di Bello (6 months); SMO dose of 50mg/kg/day in all studies.
Source: Gallimberti et al., 1992; Caputo et al., 2003, 2007 ; Nava et al., 2006 ; Di Bello et al., 1995; Leone et al., 2010.

In a double-blind, placebo-controlled pilot RCT conducted in Italy and investigating the efficacy and safety of SMO for the maintenance of abstinence, 82 AD outpatients were randomized in two groups: SMO 50 mg/kg/day divided into three daily doses or placebo three times a day. Treatment duration was 3 months. Efficacy was measured with the PDA during the treatment period, the number of drinks/day during the treatment period, and the abstinence rate. There was no clinically relevant difference in baseline characteristics between treatment groups. Results showed a significantly higher PDA in the SMO group compared with the placebo group: mean difference (95% - CI) 17.5% (10.7, 24.3), p<0.001. The number of drinks per day was significantly lower in the SMO group compared with the placebo group: mean difference (95% CI) - 4.6 drinks/day (- 6.2, - 3.0), p<0.001. The abstinence rate was significantly higher in the SMO group than in the placebo group: excess rate + 24.8%, p=0.02 (Table 2) (Gallimberti et al., 1992; Leone et al., 2010). These results thus showed efficacy of SMO in the maintenance of abstinence in AD patients.

Another double-blind, placebo controlled RCT evaluated the effect of SMO on craving for alcohol and relapse to drinking in detoxified AD outpatients. A total of 17 AD patients were randomly assigned to two groups: SMO 50 mg/kg/day (n=9) or placebo (n=8). Subjects were treated for 6 months. The alcohol craving score was significantly lower in the SMO group compared to the placebo group ($p<0.05$) at the end of the 6-month treatment period. The abstinence rate was numerically in favour of SMO but with a small effect size and not statistically significant (Table 2) (Di Bello et al., 1995).

One open-label RCT compared the efficacy of SMO with naltrexone (NTX) in maintaining abstinence from alcohol after 3 months of treatment. A total of 35 detoxified AD outpatients were randomly enrolled in one of two groups: SMO 50 mg/kg/day fractioned in three doses (18 patients); NTX 50mg/day (17 patients). There was no clinically relevant difference in baseline characteristics between treatment groups. At the end of the study, a statistically significant difference in favour of SMO was found in the abstinence rate: excess rate +31.4%, p=0.02 (Table 2), indicating that SMO is more effective than NTX in maintaining abstinence from alcohol in a 3-month treatment period (Caputo et al., 2003).

Similarly, another open-label RCT compared the efficacy of SMO (50 mg/kg/day), NTX (50 mg/day), and SMO plus NTX in maintaining abstinence. Fifty-five detoxified AD patients were randomly enrolled in three groups and treated for 3 months with SMO (n=20), SMO plus NTX (n=18), or NTX (n=17). There was no clinically relevant difference in baseline characteristics between treatment groups. At the end of treatment, abstinence was maintained by 13 patients (72.2%) in the SMO plus NTX group, 8 patients (40%) in the SMO group, and one patient (5.9%) in the NTX group. SMO was statistically significantly superior to NTX in abstinence rate (p=0.04) with a large effect size (excess rate: +34.1%; relative risk = 6.8). The SMO/NTX combination was also more effective than either drug given alone (Table 2), suggesting that the two drugs combine their different actions synergistically without suppressing the favourable effects of each other (Caputo et al., 2007).

Another open-label RCT was conducted to compare different AD treatments on the amount of alcohol intake, craving, and on biochemical measures of alcohol consumption. Eighty-six detoxified AD patients were randomly assigned to SMO (50 mg/kg fractioned in three doses, n=28), NTX (50 mg/day, n=27) or disulfiram (DSF: 200 mg/day, n=31) treatment for 12 months. There was no clinically relevant difference in baseline characteristics between treatment groups. SMO showed numerically higher abstinence rates: +16.0% vs NTX, +34.1% vs DSF (Table 2). Patients in the SMO group had significantly larger decreases in alcohol craving and in laboratory markers of alcohol abuse than did patients in the NTX and DSF groups (Nava et al., 2006).

Meta-analyses of RCTs on SMO efficacy in the maintenance of abstinence

Results of individual studies are supported by the meta-analysis performed in 2010 by The Cochrane Collaboration: SMO was superior to placebo (RR=5.35; 95%CI: 1.28-22.4; p=0.02) and to NTX (RR=2.59; 95%CI: 1.35-4.98; p=0.004) in abstinence rate after a 3 months treatment period (Leone et al., 2010). In addition, in a recent network meta-analysis including 64 trials (43 interventions), SMO was significantly more effective than placebo in the abstinence rate: odds ratio (95%CI) 2.31 (1.22 to 4.36). Moreover, SMO was better ranked than acamprosate, naltrexone and disulfiram in achieving abstinence. However, results also showed evidence of inconsistency between direct and indirect comparisons (Cheng et al., 2020) suggesting an unbalanced presence of effect modifier(s) across the network (Dias et al., 2011).

Non-controlled studies on SMO effect in the maintenance of abstinence

Five open-label and non-controlled studies investigated the effect of SMO on maintenance of alcohol abstinence treatment (Addolorato et al., 1998, 1996; Caputo et al., 2011, 2009; Maremmani et al., 2001).

An open-label, uncontrolled multicentre (19 sites) study evaluated the effect and safety of SMO in inducing and maintaining abstinence. A total of 179 AD outpatients were treated with SMO (50 mg/kg/day) for 6 months followed by a 12-month medication-free period. Patients were not detoxified and were still drinking at treatment initiation. A total of 70 patients (39%) did not complete the study. Complete abstinence during the SMO treatment was achieved in 78.0% of patients who completed the treatment phase. Of these abstainers, 43 (51%) and 30 (36%) subjects remained abstinent at 6 months and at 12 months medication-free follow-up phase, respectively (Addolorato et al., 1996).

Another open-label, uncontrolled study investigated the effect of SMO on alcohol abstinence and the risk of craving for and abuse of SMO in AD subjects with and without psychiatric co-morbidity. Forty-eight AD patients were enrolled and classified into two groups: group A (20 AD patients without psychiatric co-morbidity) and group B (28 AD patients with psychiatric co-morbidity). All patients were treated with oral SMO (50 mg/kg/day) for 12 weeks. A reduction of alcohol intake in both groups was observed ($p<0.0001$). Alcohol abstinence during the 12 weeks of treatment did not differ between the two groups at the end of treatment: abstinence rate 45% in group A compared with 50% in group B, p=0.7 (Caputo et al., 2011).

A third open-label, uncontrolled study investigated the effect of SMO on alcohol abstinence and the risk of craving for and abuse of SMO in AD patients with poly-addiction. A total of 47 AD patients was enrolled and divided into four

groups: group A (pure AD patients), group B (AD patients with a sustained full remission from cocaine dependence), group C (AD patients with a sustained full remission from heroin dependence) and group D (AD patients in a methadone maintenance treatment programme). All patients were treated with SMO (50 mg/kg/day) for three months. At the end of treatment, continuous abstinence from alcohol was maintained by 25 patients (53.2%): 9 patients (64.3%) in group A, 5 patients (50.0%) in group B, 8 patients (61.5%) in group C and 3 patients (30.0%) in group D. There were no significant differences in abstinence rates between the groups (Caputo et al., 2009).

A fourth open-babel, uncontrolled study investigated the effect of a different fractioning of SMO (50mg/kg/day) in the maintenance of abstinence in AD patients not responding to the usual three SMO administrations per day. A total of 154 AD patients were treated with SMO (50mg/kg/day) divided in three administrations for 8 weeks (phase 1). Patients who were not abstinent at the end of the phase 1 were administered the same daily SMO dose but divided in six administrations for a subsequent 8-week period (phase 2). Of the 154 patients, 115 completed phase 1; 78 (67.8%) of these patients began and maintained abstinence (group A) while 37 subjects (32.2%) continued to drink alcohol (group B) showing craving scores that were significantly higher than group A at the end of phase 1 ($p < 0.001$). In these group B patients, the adapted fractioning of the study medication in phase 2 was associated with a significant reduction in craving ($p< 0.005$) and 26 of these 37 patients (70.2%) began and maintained abstinence. Moreover, no significant difference in final craving score between group A and B was observed. Within the limits of an open study, these data suggest that non-responder subjects to the conventional fractioning of SMO may benefit from a more frequent fractioning of the drug (Addolorato et al., 1998).

A final open-label, uncontrolled study investigated the effect of SMO in treatment-resistant chronic AD patients. Thirty-five treatment-resistant AD patients were administered SMO doses ranging between 25 and 100 mg/kg/day depending on patients' clinical response for one year. A total of 60% of these patients successfully completed the protocol and were considered responders: 11.4% showed complete abstinence (full responder patients); 14.3% strongly reduced their alcohol intake (partial responder patients), 34.3% were still in treatment after one year, and 40.0% were non-responders. The retention rate under treatment of the studied sample was statistically higher than that found during the last treatment of the same subjects (Maremmani et al., 2001).

Conclusion on SMO efficacy in the maintenance of abstinence

The efficacy of SMO in the maintenance of abstinence was initially investigated in 10 studies, including five exploratory RCTs. Data converge and support a beneficial effect of SMO in the maintenance of abstinence, even in patients with psychiatric comorbidity and in patients with a history of poly-addiction. However, no phase III trial was conducted to confirm these positive results and the RCTs were generally small with sample sizes ranging from 17 to 82 patients (total n=244). Almost all of them used only one fixed dose of SMO, and none of the RCTs investigated the sustainability of the SMO effect after treatment discontinuation.

Furthermore, serious heterogeneity of the SMO effect size was observed across studies in the maintenance of abstinence and the source of this heterogeneity was not investigated. This heterogeneity is not specific for the treatment of AD with SMO. In a meta-regression analysis including 51 RCTs, heterogeneity of treatment effect of medications approved for the treatment of alcohol dependence (naltrexone and acamprosate) was substantial and the effect size was significantly negatively correlated with the placebo response in the study population (Litten et al., 2013). Recently, there has been a convergence of evidence 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 at baseline and with less than 14 consecutive days of abstinence before randomization (‘high severity population’) than in the complement population with Low or Medium DRL at baseline or more than 14 consecutive abstinent days before randomization (“mild severity population”) (Gual et al., 2013; Gueorguieva et al., 2012, 2011; Mann et al., 2016; Pierce et al., 2018; van den Brink et al., 2018, 2013). Furthermore, analyses at patient level showed that the placebo response in RCTs for AD was dependent on the treatment duration: the longer the treatment duration, the lower the placebo response (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). It would thus be of interest to explore the effect of these covariates (population severity and treatment duration) on SMO efficacy in the maintenance of abstinence.

Safety of SMO in the treatment of alcohol dependence

Addolorato et al. (2019) performed a review on the safety of oral SMO in the treatment of AD using clinical studies and pharmacovigilance data of the SMO solution Alcover®. Both, studies on the efficacy of SMO for the treatment of AWS and maintenance of abstinence were included in the analysis. A total of 2,547 eligible patients were exposed to several dose regimens of SMO in these clinical studies (Table 3). Overall, 637 common (non-serious) treatment-emergent adverse events (TEAEs) were reported. Of these, 138 TEAEs were reported in 1,150 patients exposed to SMO ≤50 mg/kg/day (11.5%) and 499 TEAEs were reported in 1,397 patients exposed to SMO >50mg/kg/day (35.7%), suggesting the presence of a dose-effect relationship. Dizziness, vertigo, and drowsiness were the most consistently reported adverse effects (9.2-13.2% of patients). Vomiting, diarrhoea, and nausea were observed in 0.1-3.0% of patients. In general, these TEAEs did not require interruption of treatment, since dizziness disappeared spontaneously after the first doses, and more than 50% of TEAEs disappeared within the first month of treatment. No serious TEAEs and no deaths attributable to the use of SMO have been reported in these 2,547 patients exposed to oral SMO (Table 3) (Addolorato et al., 2019). Abuse/misuse cases were found only in AD patients with severe psychiatric comorbidities or polysubstance dependence with 64 cases of abuse/misuse in 552 patients (11.6%) in clinical studies (Addolorato et al., 2019). Nevertheless, cases of abuse did not result in serious adverse events (Caputo et al., 2011, 2009).

Table 3. Safety of oral SMO in alcohol-dependent patients* (from Addolorato et al., 2019)

	SMO ≤50 mg/kg/day (% of patients)	**SMO >50 mg/kg/day (% of patients)**
Patients exposed to SMO	1150 (100%)	1397 (100%)
Number of TEAEs §	138 (11.5%)	499 (35.7%)
Vertigo/dizziness/drowsiness	110 (9.2%)	185 (13.2%)
Vomiting	5 (0.4%)	42 (3.0%)
Diarrhea	4 (0.3%)	30 (2.1%)
Nausea	1 (0.1%)	25 (1.8%)
Patients with serious TEAEs §	0 (0.0%)	0 (0.0%)

* Combined data from 43 clinical studies found in 44 articles or reports of the biomedical literature
§TEAE, Treatment Emergent Adverse Event

The pharmacovigilance database for Alcover® in Italy and Austria includes 299,013 patients exposed to SMO for the treatment of AWS and/or maintenance of abstinence from 1992 to October 2017. Common, non-serious adverse events (AEs) were reported in 17 Austrian patients (0.3%; mainly vertigo, nausea, and diarrhoea) and 68 Italian patients (0.02%; mainly vertigo, nausea and sopor). No

fatal AE was reported in this pharmacovigilance database, but there were seven cases of overdose, one case of diversion/criminal misuse, two cases of SMO dependence, and 10 cases of abuse/misuse (Addolorato et al., 2019).

Overall, oral SMO in the treatment of AD has been well-tolerated both in clinical trials and in standard clinical practice in Italy and Austria (Addolorato et al., 2019) but the occurrence of non-serious TEAEs seemed to be dose-dependent. Rare cases of abuse, dependence and diversion have been reported in the pharmacovigilance database and AD patients with severe psychiatric comorbidities or polysubstance dependence showed a higher risk of abuse/misuse (Addolorato et al., 2019). Since these risks cannot be neglected, a new oral formulation of SMO was developed that aims to minimize the risk of abuse, misuse, and criminal use of SMO.

New abuse/misuse deterrent SMO formulation

SMO is transparent, odourless, and slightly salty when dissolved in water and may become undetectable if not formulated. Therefore, an oral dry granules formulation with abuse/misuse deterrent properties (Hopveus®) has been developed. The granules are flavoured (apple), partly insoluble, floating, effervescent and filled in sachets. They are noticeable when put in a drink preventing the risk of criminal misuse (Figure 5).

Figure 5. Behaviour of SMO 0.75g abuse-misuse deterrent formulation (called Alcover Granules) in still water and Coca-cola®

The granules also present a low SMO load and an important and difficult to ingest quantity of granules is needed to reach SMO toxic doses. For instance, 46 to 206 sachets of SMO 1.25g would need to be ingested to reach the average self-administered daily dose reported in GHB dependent patients (Kamal, 2016). The bioequivalence of the granules formulation with Alcover® was demonstrated (European Medicines Agency, 2020) however, the safety of this new formulation needed to be tested in a large RCT.

AIMS OF THIS THESIS

Given the above identified limitations, the purpose of this thesis is:

i) to test the efficacy and safety of SMO in the maintenance of abstinence in AD patients in a large confirmatory RCT,
ii) to investigate the SMO dose-response relationship in the maintenance of abstinence in AD patients in a large RCT,
iii) to test the safety of the new SMO oral granules formulation with abuse/misuse deterrent properties,
iv) to systematically test the effect of population severity and treatment duration on placebo response and on SMO efficacy in the maintenance of abstinence in AD patients, and
v) to analyse the alcohol-attributable morbidity and mortality in the patient population where SMO seems to be (most) effective.

The specific research questions are:

1. What is the relationship between SMO dose and SMO efficacy in the maintenance of abstinence in AD patients? (**Chapter 2**)
2. Can the new solid granules formulation in sachets prevent the risk of abuse and/or misuse of SMO in AD patients? (**Chapter 2**)
3. Is the efficacy of SMO in the maintenance of abstinence in AD patients confirmed and sustained post treatment? (**Chapter 3**)
4. Are population severity and treatment duration effect modifiers of SMO and/or predictors of the placebo response in the maintenance of abstinence in AD patients? (**Chapter 2, 3, 4, 5)**
5. What is the health burden of AD in the patient population in which SMO is (most) effective? (**Chapter 5**)

Chapter 2 presents the results of a Phase IIb placebo controlled RCT testing the efficacy and safety of a maintenance of abstinence treatment with SMO in AD patients comparing four doses of the new SMO abuse/misuse-deterrent formulation (Hopveus®). The effects of population severity and treatment duration on SMO treatment effect are also explored in this Phase IIb study.

Chapter 3 reports the results of a large Phase III double-blind placebo controlled RCT aiming to confirm SMO efficacy and safety in the maintenance of abstinence in AD patients and at investigating the sustainability of SMO efficacy post-treatment. In addition, heterogeneity of the SMO treatment effect and generalizability of results are investigated in this Phase III study.

In **Chapter 4**, a meta-regression analysis is used to systematically study the effects of population severity and treatment duration on the placebo response in the maintenance of abstinence in double-blind RCTs conducted in AD patients.

In **Chapter 5**, a network meta-regression analysis is used to systematically explore the effects of population severity and treatment duration on SMO efficacy in the maintenance of abstinence in RCTs conducted in AD patients. In addition, SMO efficacy in each severity population is analysed with a network meta-analysis.

Chapter 6 analyses the burden of AD in the patient population where SMO seems to be particularly effective (i.e., AD subjects with a Very High DRL at baseline).

In **Chapter 7**, results of Chapter 2 through Chapter 6 are discussed.

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CHAPTER 2

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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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 2.25g 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.

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 registered 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 γ-hydroxybutyric acid (GHB), a short-chain fatty acid that occurs naturally in the mammalian brain. GHB binds with low affinity to GABA subtype B (GABAB) 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 50mg/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 2.25g 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.

EXPERIMENTAL PROCEDURES

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/m², who met ≥ 4 DSM-IV-R criteria for AD, who confirmed ≥ 7 drinking days including ≥ 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 ≥ 5 drinks per day in males and ≥ 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 ≥ 24 hours 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.

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.

Study procedures

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 (0.75g t.i.d., 1.25g t.i.d., 1.75g t.i.d., and 2.25g 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 1.25g t.i.d. and the 1.75g 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.

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).

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).

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 to12), 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 40g/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 (ALAT), aspartate aminotransferase (ASAT), mean corpuscular volume (MCV), γ-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.

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 α=0.0125, 99 patients in each treatment group would provide a power of 80%. The α=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, 0.75g, 1.25g, 1.75g, 2.25g 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.

RESULTS

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 (Figure 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.

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 protocol 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 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).

Figure 1. Patient flow chart

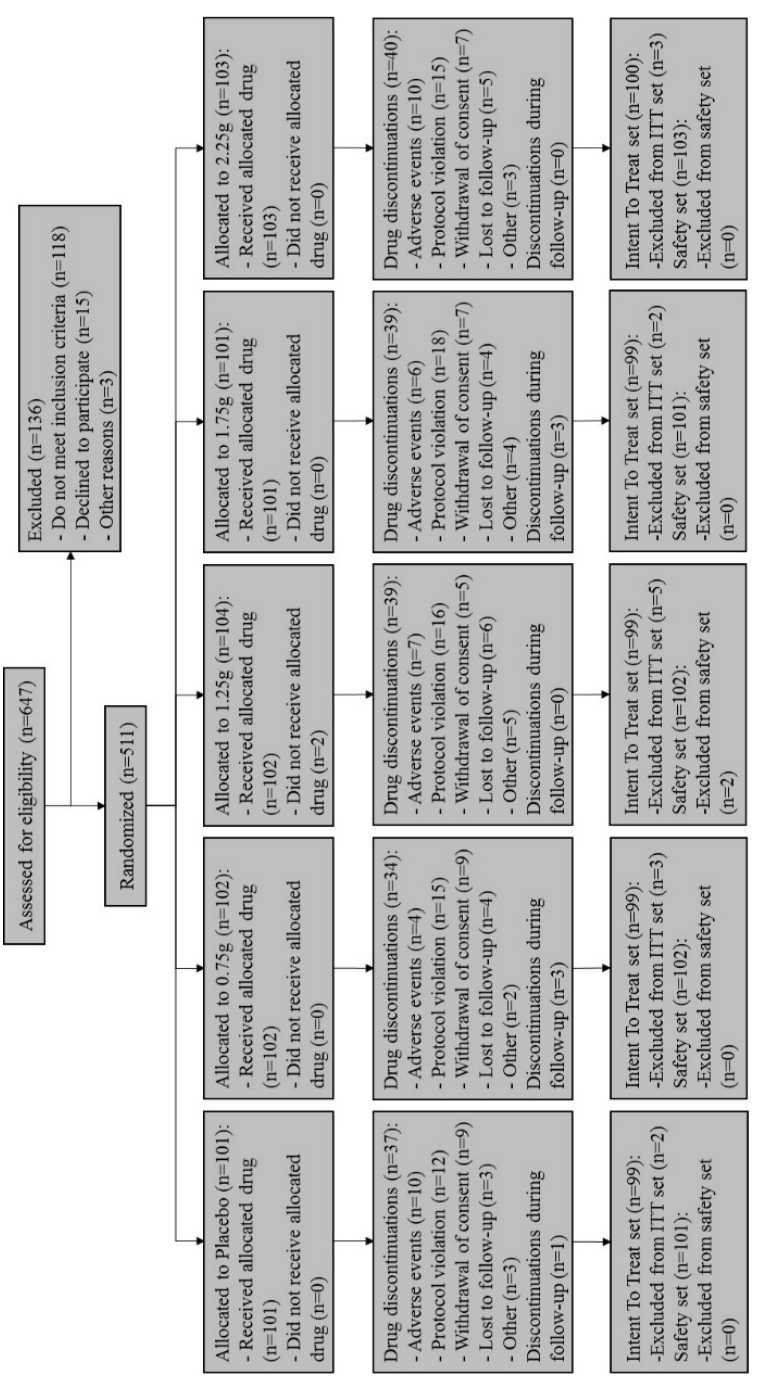


Table 1. Demographics and baseline clinical characteristics: mean (SD)

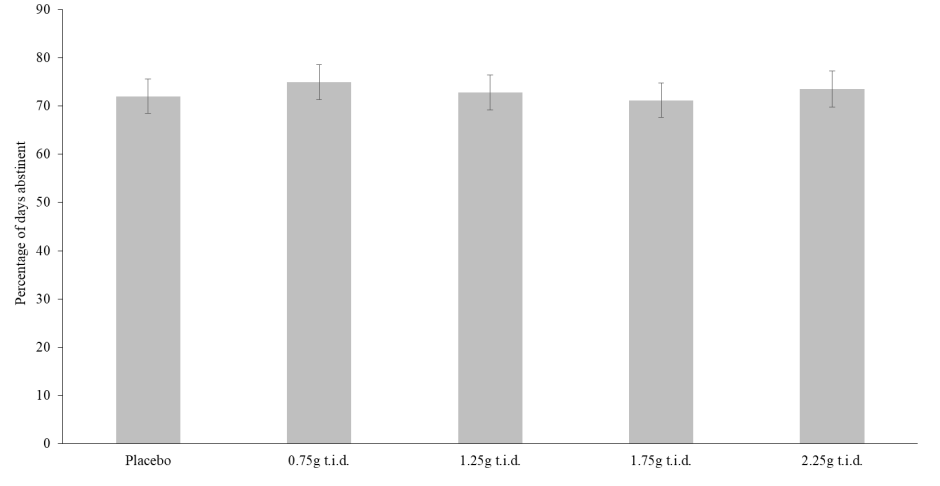
	Placebo	**0.75g**	**1.25g**	**1.75g**	**2.25g**
N	99	99	99	99	100
Age	48.3 (11.2)	47.1 (11.9)	47.4 (10.4)	48.1 (11.6)	47.7 (11.2)
Gender: females n (%)	32 (32.3)	22 (22.2)	24 (24.2)	22 (22.2)	24 (24.0)
Weight	75.3 (12.4)	75.1 (14.9)	76.9 (12.3)	78.9 (13.8)	75.6 (13.6)
BMI	25.3 (3.3)	24.4 (3.6)	25.3 (3.2)	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: γ-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

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, 2.25g 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%).

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



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.

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.
Percentage of Days Abstinent (PDA) 12-week treatment period				
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
Number of HDD – treatment period				
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
OCDS - Compulsive Subscale Score - End of treatment				
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
OCDS - Resistance/Impairment Subscale Score - End of treatment				
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
%CDT – End of treatment				
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
Abstinence rate – one week follow-up				
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
Number of HDD – one week follow-up				
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
Percentage of subjects with no HDD – one week follow-up				
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
Time to relapse – one week follow-up				
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

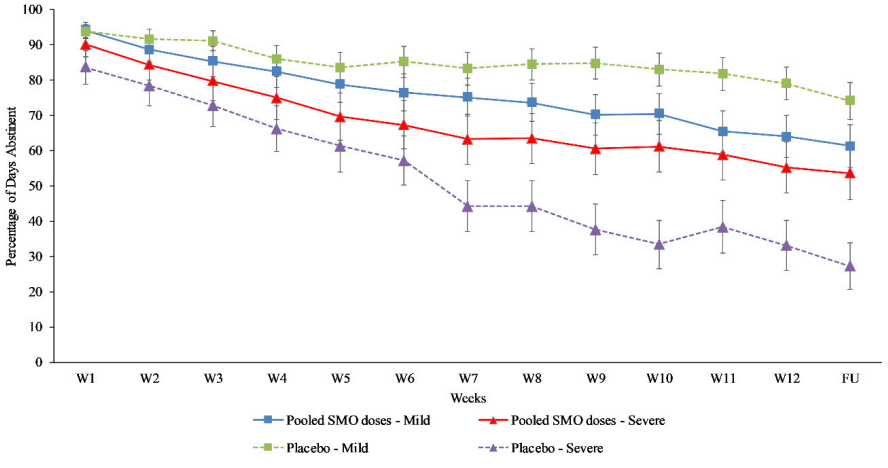
Dose-response relation

Dose-response analyses showed that treatment response in terms of PDA was negatively correlated with bodyweight only in the SMO 0.75g 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 18mg/kg/day in the ITT population (composed for 68% of Low or Medium DRL patients) and 60mg/kg/day in patients with a High or Very High DRL at baseline (inverted U-shape curve is presented in Figure S1).

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 $d=0.41$), 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 (Figure 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 (Figure 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%, $p<0.0001$; Figure 3).

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



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 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 2.25g t.i.d.), epilepsy (SMO 1.25g t.i.d.), loss of consciousness (SMO 2.25g t.i.d.), and discomfort (2.25g 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 1,746 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 0.75g t.i.d. group, 3.0 points (SD=2.7) in the 1.25g t.i.d. group, 3.3 points (SD=0.6) in the 1.75g t.i.d. groups, and of 4 points (SD=2.7) in 2.25g t.i.d. group.

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 (≥ 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.

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., 2003, 2007; Gallimberti et al., 1992; Leone et al., 2010; Maremmani 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 1.75g t.i.d. and 0.75g 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). Furthermore, 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 (European Medicines Agency, 2012; Gual et al., 2013; Gueorguieva et al., 2012, 2011; Mann et al., 2016, 2013; Reynaud et al., 2017; van den Brink et al., 2018, 2014, 2013). 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., 2014, 2013). 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 (130mg/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 randomisation, 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 (50mg/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 Kinnov 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 Bioprojet, CV Sciences, and Ethypharm, and has received sponsorship to attend scientific meetings, speaker honoraria or consultancy fees from Bioprojet, D&A Pharma, Ethypharm, Kinnov Pharmaceuticals and Lundbeck. He is also member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative (ACTIVE), which was supported in the last three years by Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Ethypharm, Indivior, Lundbeck, Mitsubishi, and Otsuka.

Antoni Gual received funding from Novartis to conduct a trial on cocaine dependence and fees as speaker from Alkohol & Samfund.

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); 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.

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CHAPTER 3

Sodium oxybate for the maintenance of abstinence in alcohol dependent patients: An international, multicenter, randomized, double-blind, placebo-controlled trial

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ABSTRACT

Background: Sodium oxybate (SMO) has been shown to be effective in the maintenance of abstinence in alcohol-dependent patients in a series of small randomized controlled trials. These results needed to be confirmed by a large trial investigating the treatment effect and its sustainability after medication discontinuation.

Aims: To confirm the SMO effect on (sustained) maintenance of abstinence in detoxified alcohol-dependent patients.

Methods: Large double-blind, randomized, placebo-controlled trial in detoxified adult alcohol-dependent outpatients (80% men) from 11 sites in four European countries. Patients were randomized to 6 months SMO (3.3-3.9 g/day) or placebo followed by a 6-month medication-free period. Primary outcome was the cumulative abstinence duration (CAD) during the 6-month treatment period defined as the number of days with no alcohol use. Secondary outcomes included CAD during the 12-month study period.

Results: Of the 314 alcohol-dependent patients randomized, 154 received SMO and 160 received placebo. Based on the pre-specified fixed-effect two-way analysis of variance including the treatment-by-site interaction, SMO showed efficacy in CAD during the 6 months treatment period: mean difference +43.1 days, 95% confidence interval [17.6 – 68.5; p=0.001]. Since significant heterogeneity of effect across sites and unequal sample sizes among sites (n=3 to 66) were identified, a site-level random meta-analysis was performed with results supporting the pre-specified analysis: mean difference +32.4 days, p=0.014. The SMO effect was sustained during the medication-free follow-up period. SMO was well-tolerated.

Conclusions: Results of this large randomized controlled trial in alcohol-dependent patients demonstrated a significant and clinically relevant sustained effect of SMO on CAD.

Trial registration: ClinicalTrials.gov Identifier: NCT04648423

INTRODUCTION

Alcohol dependence (AD; World Health Organization, 2016) occurs in 2.6% of people aged 15+ years worldwide (World Health Organization, 2018) and can result in a reduction of life-expectancy by up to 35 years as compared with the general population (Rehm et al., 2018).

One of the treatment goals for AD is abstinence (European Medicines Agency, 2010). Currently, disulfiram, acamprosate and naltrexone are registered for the maintenance of abstinence (MoA) in AD patients. Although effective on the group level, effects sizes are limited, and many AD patients fail to respond to these medications (European Medicines Agency, 2010; van den Brink et al., 2018). Therefore, additional pharmacological treatments are needed.

Sodium oxybate (SMO) as an oral solution has been approved in Italy and Austria for the treatment of alcohol withdrawal syndrome and the MoA since 1991 and 1999, respectively (van den Brink et al., 2018). SMO is the sodium salt of γ-hydroxybutyric acid (GHB), a short-chain fatty acid that is naturally synthesized in the mammalian brain. GHB is a gamma-aminobutyric acid (GABA) receptor agonist which binds with low affinity to GABA subtype B receptors (and indirectly with the GABA subtype A receptors) and with high affinity to GHB-specific receptors (Keating, 2014). Given that the pharmacological profile of GHB has some similarities to that of alcohol, one proposed mechanism of SMO in the treatment of AD is its ability to mimic some effects of alcohol in the brain particularly to reduce craving while abstinent (Kamal et al., 2016; Keating, 2014). SMO 50mg/kg/day showed evidence of efficacy compared with placebo or naltrexone in the MoA in AD patients in a series of open label and blinded randomized controlled trials (RCTs) and was positively evaluated for this indication in a Cochrane review (Caputo et al., 2007, 2003; Gallimberti et al., 1992; Leone et al., 2010). However, studies were generally small with sample sizes ranging from 16 to 86 patients and they did not investigate the sustainability of the SMO effect after treatment discontinuation.

The present RCT (GATE 2) in 314 AD patients aimed to confirm the efficacy and safety of oral SMO in the MoA. Secondary aims included the assessment of sustained SMO effects during the 6-month medication free period immediately following the 6-month treatment period and monitoring the risk of SMO dependence.

METHODS

Design

This double-blind, placebo-controlled, outpatient RCT with balanced randomization (1:1) included patients from 11 sites in Austria, Germany, Italy, and Poland. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practices, and the European guidelines for the development of AD treatment (Plinius Maior Society, 1994). The study was approved by ethics committees/institutional review boards at all sites and written informed consent was obtained from all patients. The trial is registered in ClinicalTrials.gov (NCT04648423).

In a previous review by Skala et al. (2014) on SMO in the treatment of AD some preliminary information on the GATE 2 trial was provided. The detailed study protocol is provided in Supplement 2.

Participants

Inclusion criteria were as follows: age 21-75 years, a clinical diagnosis of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and International Classification of Diseases, 10th Revision (ICD-10) AD based on an AD checklist, a Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers (CAGE; Ewing, 1984) score ≥ 2, a Munich Alcoholism Test (MALT) (Feuerlein et al., 1979) score ≥ 11, availability of a responsible relative or caregiver, and a successful detoxification, including a 10-day treatment period and a subsequent 10-day untreated abstinent period. Exclusion criteria were as follows: relapse during the detoxification period; renal failure, severe respiratory problems, heart failure; hepatic encephalopathy stage II-IV; drug dependence; history of epilepsy or epileptic seizures not properly controlled by established anti-epileptic treatment; severe psychiatric disorder requiring medical treatment; treatment with clonidine, disulfiram (after the end of the detoxification period), haloperidol, bromocryptine, serotonine re-uptake inhibitors or other serotoninergic agents; female subjects who cannot assure not to become pregnant during the study; pre-existent hypersensitivity to GHB.

Treatments/Interventions

The statistical department of the clinical research organization involved in the study established the allocation sequence. The randomization was stratified by site and the random numbers were computer-generated using a pseudo random uniform distribution with a block size of 4 patients to ensure a good balance of

treatment groups within sites. The study medications (sodium oxybate and placebo) were supplied by the sponsor of the study and packed in identical bottles of 140ml, numbered according to the allocation sequence. The investigators assigned the eligible subjects to interventions using the lowest unassigned number available in the site. Sponsor, investigators, and patients were blind to treatment assignment during the full study period. Blinding was not broken for any patient during the trial. SMO (175mg/ml) and placebo oral solutions were identical in appearance and taste.

Procedures

Randomized patients entered a 6-month treatment phase with SMO or placebo followed by an abrupt discontinuation of the study medication and a 6-month medication-free period. Patients self-administered the medication at the dose of 17.5 ml/day divided into three doses for patients with a bodyweight ≤ 65 kg and 20 ml/day in three doses for others. In an amendment, these doses were increased to 19 ml/day for patients ≤ 65 kg and 22.5 ml for others to be closer to the approved posology in Italy and Austria (50mg/kg/day). Out of 314 randomized patients, the original and the revised dose regimen were received by 11 and 303 patients, respectively. Standard psychosocial interventions at the individual sites were provided at each visit to enhance motivation and abstinence from alcohol. Study visits were planned for every month in the treatment phase and every 2 months during the follow-up phase. Patients received a diary card to record drinking and non-drinking days.

Measures

Baseline data included the following: date of birth, gender, race, height, body weight, ICD-10 AD diagnosis, DSM IV AD diagnosis, CAGE score, MALT score, mean corpuscular volume (MCV) and γ-glutamyl transferase (GGT).

The primary efficacy outcome was the Cumulative Abstinence Duration (CAD) during the 6-month treatment phase. CAD was the primary endpoint recommended in the Plinius Maior Society guidelines for the evaluation of treatments of alcohol dependence (Plinius Maior Society, 1994). European guidelines have since then evolved from 2010 onwards and the proportion of patients continuously abstinent throughout the treatment period (continuous abstinence rate - CAR) is now the recommended primary endpoint for studies on MoA (European Medicines Agency, 2010). However, at the time that the GATE 2 study was designed (2000), CAD was still considered the standard primary outcome for studies on the treatment of AD. For example, CAD was widely utilized as the (co-)primary endpoint in acamprosate trials, including those that were used as pivotal evidence in the registration process of the drug for MoA in

the European Union (Spanagel and Mann, 2005). Consequently, it was also defined as a primary outcome in the Cochrane meta-analysis of acamprosate for the MoA in AD patients (Rösner et al., 2010a). CAD is still considered an important secondary endpoint by the European Medicines Agency (2010). In the current study, CAD was calculated as the number of days with no alcohol use (Plinius Maior Society, 1994). At treatment group level, CAD measures the differences in CAR as well as the differences in abstinence duration in relapsing patients. It can therefore be conceptualized as a composite endpoint with the current recommended primary endpoint as one of its components. In GATE 2 and due to uncertainty regarding accurate reporting of duration of relapses, if a relapse occurred since the last visit and was reported by the patient at a visit, the entire month before the visit was considered as a period of relapse, irrespective of the declared duration of the relapse (Besson et al., 1998; Gual and Lehert, 2001; Pelc et al., 1997; Plinius Maior Society, 1994; Poldrugo, 1997; Tempesta et al., 2000; Whitworth et al., 1996). Relapse was defined as any alcohol consumption.

Key secondary outcome measures include the following: the CAD during the 12-month study period, the CAR at the end of the 6-month treatment phase and at the end of the 12-month observation period, the time to first relapse, the MCV and GGT at the end of 6 months treatment, and the compliance with the assigned treatment. CAR definition was compliant with the definition of the European guidelines (European Medicines Agency, 2010). Compliance with assigned treatment was defined as sufficient if the total actual consumption of the medication was higher than 75% of the total intended consumption.

Main safety assessments included the evaluation of Adverse Events (AEs) and the Lubeck Craving Recurrence Risk questionnaire (Veltrup, 1994, item 1 & 2) to evaluate craving for the study medication. Patients were asked to define the frequency of their desire for the study medication using the following categories: 1) (nearly) continuously from getting up in the morning until going to sleep; 2) approximately every 15-30 minutes; 3) approximately every 30-60 minutes; 4) every 2-3 hours; 5) more seldom than every 2-3 hours; and 6) never.

Statistical methods

The sample size calculation was based on a group difference between placebo and SMO of 20 days of CAD during the treatment period and a standard deviation (SD) of 60 days. Using the assumed variability and a two-sided α=0.05, 143 patients in each treatment group would provide a power of 80%. Given the randomization procedure with block size of 4 patients and to reduce the risk of having a site with no patient in one treatment group, it was decided to increase the sample size to up to 160 patients per group.

All analyses were conducted in the Intent-to-Treat (ITT) population which includes all patients who received at least one dose of the allocated drug.

CAD was analyzed in accordance with the pre-specified analysis in the protocol, including a fixed-effect 2-way analysis of variance (ANOVA) with terms for treatment, site and treatment-by-site interaction. Heterogeneity of effect across sites was first identified by graphical display of the results for each individual site. Consequently, to explore generalizability of results and to substantiate the robustness of the point estimate of the treatment effect, mixed-effect models with treatment as fixed effect and the site-by-treatment interaction as random effects were fitted to the data (Barr et al., 2013; Feaster et al., 2011; Senn, 2021). Unfortunately, these models faced convergence issues in the estimation of the variance of the random terms. This commonly occurs with small-to-medium data sets and/or in complex models with several terms and/or with models including a categorical variable (such as site) as random effect and with a relatively small number of categories (Barr et al., 2013; Bates et al., 2018, 2015; Eager and Roy, 2017). In this context and as an alternative method to the mixed-effect models, site-level random effect meta-analyses were fitted to the data for both CAD at the end of 6-month treatment and CAD at the end of the 12-month study period. Treatment effects were computed at site level and were then pooled using a random-effect meta-analysis model. Heterogeneity was tested with the Cochran Q test and was quantified with the I2 index. The relationship between treatment effect and placebo response in CAD in each site was post-hoc investigated with a linear regression model.

CAR was analyzed using risk difference with 95% confidence intervals (CIs). Time to the first relapse during the treatment period was analyzed with Kaplan-Meier estimates. MCV and GGT were summarized with descriptive statistics (geometric mean). Mean difference in the compliance with the assigned treatment was tested with a Student's t-test. The effect of the site on the treatment effect was a posteriori investigated with a two-way ANOVA with site-by-treatment interaction for compliance as outcome and with a site-level meta-analysis for CAR as outcome.

Dropout and missing data were assumed to be missing not at random and were considered as relapse to alcohol for CAD, CAR, and time to first relapse. This assumption was selected because relapse was the main documented reason for dropout in previous trials (Balldin et al., 2003; Geerlings et al., 1997; Paille et al., 1995; Pelc et al., 1997; Poldrugo, 1997; Sass et al., 1996; Wiesbeck, 2001). MCV and GGT at end of treatment as well as compliance with assigned treatment were analyzed based on observed values. A sensitivity analysis was conducted on the primary endpoint with missing data assumed to be missing at random and using multiple imputation.

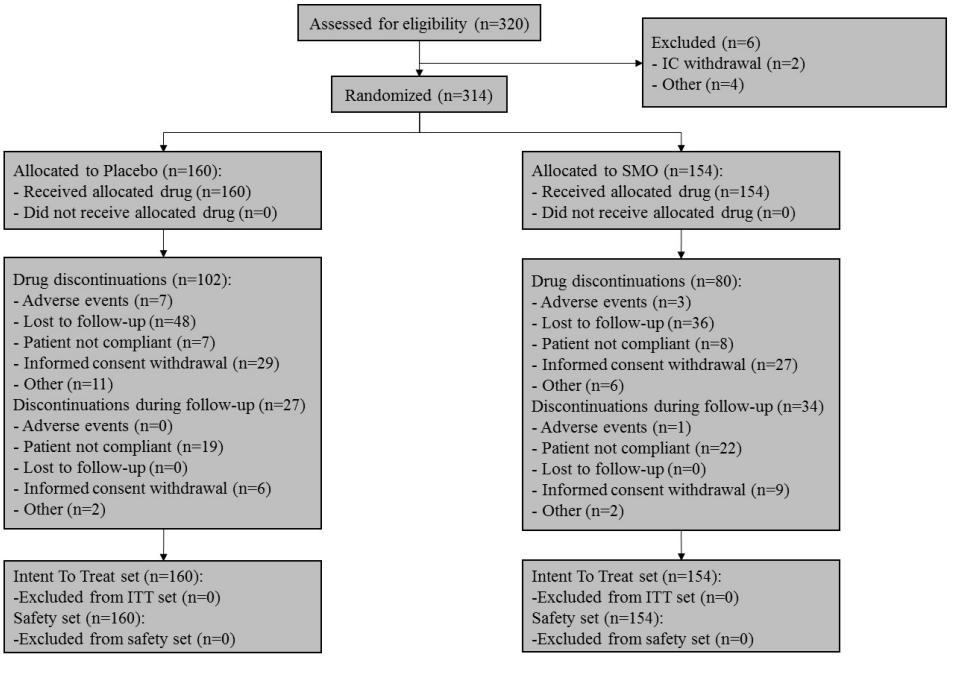
All AEs were coded according to the Medical Dictionary for Regulatory Activities dictionary. The proportions of patients that reported AEs were tabulated by group and compared by means of the chi square or the Fisher's exact probability test. For additional information on the above analyses, see Supplements 1 and 2.

The principal statistical software used was SAS®, Version 9.4. PROC MIXED was used for performing fixed effect ANOVA and mixed effects models as well as site-level random effect meta-analysis on the primary endpoint.

RESULTS

From July 2001 to March 2011, 320 subjects were screened and 314 participants were included in the ITT population, 154 were randomized to receive SMO and 160 to receive placebo. A total of 182 of the 314 randomized patients (58.0%) did not complete the 6-month treatment phase. Non-completion rates were lower in the SMO than in the placebo group both at the end of treatment (52% vs 64%) and at the end of study period (74% vs 81%) (Figure 1).

Figure 1. Patient flow chart



There were no clinically relevant differences in baseline demographic or clinical characteristics between the two groups (Table 1).

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

	SMO	Placebo
N	154	160
Age (years)	44.3 (8.7)	44.5 (9.8)
Gender: females n (%)	33 (21.4)	31 (19.4)
Race n (%)		
White	150 (97.4)	158 (98.8)
Other	4 (2.6)	2 (1.2)
Height (cm)	172.4 (8.7)	174.0 (7.7)
Body mass index (kg/m^2)	25.3 (3.7)	25.4 (4.1)
Alcohol dependence diagnosis		
ICD-10 [a]	5.3 (1.0)	5.4 (0.9)
DSM-IV [a]	6.1 (1.3)	6.3 (1.1)
CAGE score	3.5 (0.7)	3.5 (0.6)
MALT 1 score	2.0 (3.0)	2.4 (3.0)
MALT 2 score	19.2 (2.9)	19.2 (3.3)
MALT 1+2 score	21.2 (4.5)	21.5 (4.6)
Mean corpuscular volume (fL) [b]	94.4	94.6
γ-glutamyl transferase (U/L) [b]	46.5	43.9

CAGE: Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers; MALT: Munich Alcoholism Test; MALT 1 evaluates the presence of polyneuropathy, delirium tremens and/or liver disease with four points score per each positive answer. MALT 2 evaluates 24 items with one point score per each positive answer;

[a] number of alcohol dependence diagnosis criteria met

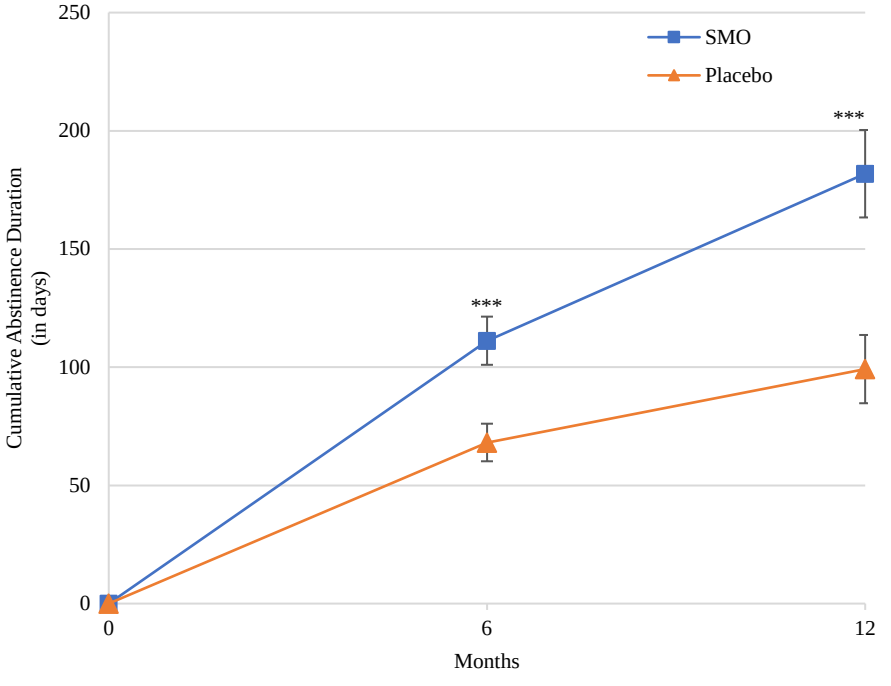
[b] geometric mean

Primary endpoint

The adjusted mean CAD during the 6-month treatment period was significantly higher in the SMO group than in placebo arm in both the fixed-effect model (adjusted mean difference +43.05 days, p=0.001) and the site-level random effect meta-analysis (mean difference +32.37 days, p=0.014) (Figure 2 and Table 2).

Results of the sensitivity analysis with multiple imputation supported the pre-specified analysis (fixed-effect model: adjusted mean difference +27.55 days, p=0.032). Due to a negative estimated Tau^2, it was not possible to provide multiple imputation results for the site-level random effect meta-analysis.

Figure 2. Adjusted mean CAD over the study period



Bars indicate standard error; ***: $p \leq 0.001$

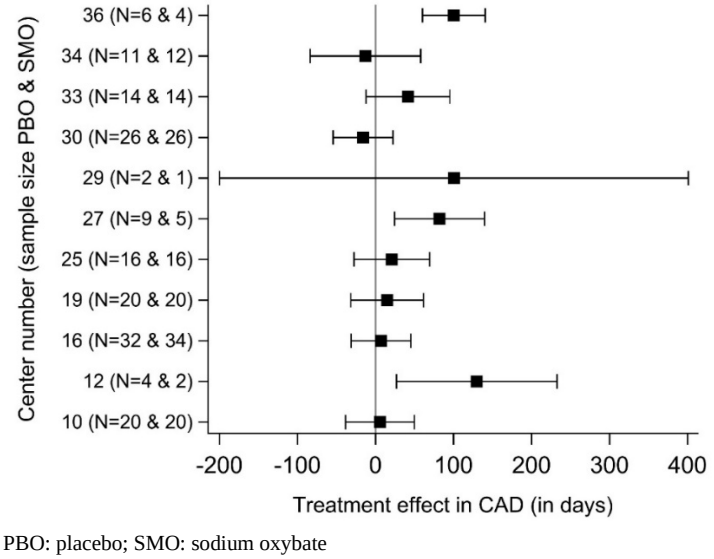
The site fixed effect on the CAD was not significant (p=0.40), but a potential treatment-by-site interaction was identified (p=0.16). Interestingly, in the meta-analysis model the Cochran Q test was highly significant (p=0.001) and substantial heterogeneity of the treatment effect across sites was identified (I2=60.8%, 95% CI: 24.2-79.7% - Figure 3).

Table 2. CAD during the 6-month treatment period and during the 12-month study period

In days	**SMO (N=154)** Adj. mean (SE)	**Placebo (N=160)** Adj. mean (SE)	**Adj. mean difference** (95% CI)	**p-value**
CAD during the 6-month treatment period				
Fixed-effect model				
Pre-specified analysis	111.20 (10.19)	68.15 (7.95)	43.05 (17.61, 68.49)	0.001
Sensitivity analysis	148.20 (9.53)	120.65 (8.33)	27.55 (2.47, 52.63)	0.032
Random effect meta-analysis	NA	NA	32.37 (6.45, 58.28)	0.014
CAD during the 12-month study period				
Fixed-effect model	181.84 (18.50)	99.19 (14.44)	82.65 (36.47, 128.83)	<0.001
Random effect meta-analysis	NA	NA	58.04 (8.54, 107.53)	0.022

CAD: Cumulative Abstinence Duration; adj.: adjusted; SE: standard error; CI : confidence interval; NA : not available

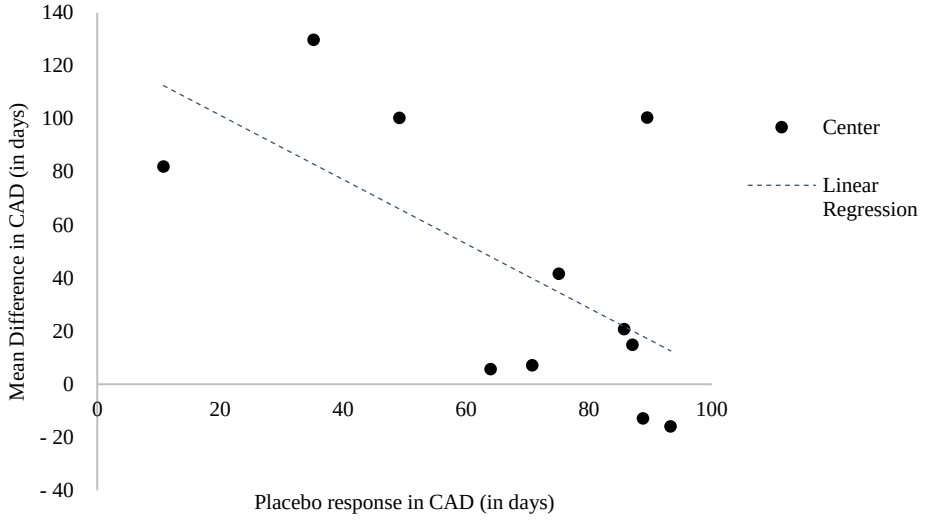
Figure 3. Site-specific treatment effects (95% CI) in CAD during the 6-month treatment period



PBO: placebo; SMO: sodium oxybate

The estimated treatment effect across sites varied from -16 days to +130 days of CAD and was negatively correlated (r=-0.63; p=0.04) with the placebo response in the sites (Figure 4). The treatment effect was numerically in favor of SMO in 9 of the 11 sites (Figure 4) and significantly in favor of SMO in two sites (Supplemental Table S2).

Figure 4. Mean difference in CAD during the 6-month treatment period and mean placebo response in each site



Secondary endpoints

The adjusted mean CAD at the end of the 12-month observation period was in favor of SMO: adjusted mean group difference +82.65 days (p<0.001) in the fixed-effect model and mean group difference +58.04 days (p=0.022) in the random effect meta-analysis model (Table 2; Figure 2).

The CAR was 25.3% in SMO group and 20.0% in placebo group (p=0.25) at the end of the 6-month treatment period and 15.6% in SMO group compared to 10.6% in placebo group (p=0.19) at the end of the observation period (Supplemental Table S3 and Table S4). The random effect meta-analysis of CAR provided similar results. The median time to first relapse during the treatment period was 77 days in the SMO group compared to 46 days in the placebo arm (difference + 31 days; p=0.13).

Regarding MCV and GGT, values at end of treatment were similar in both treatment groups and improved similarly in both treatment groups compared with screening: mean GGT of 33.4 U/L at day 180 (vs 46.5 U/L at screening) in SMO

group and 30.6 U/L at day 180 (vs 43.9 U/L at screening) in placebo group; mean MCV of 91.0 fL at day 180 (vs 94.4 fL at screening) in SMO group and 92.0 fL at day 180 (vs 94.6 fL at screening) in placebo group.

Compliance was high in both groups and the mean difference was not significantly different: mean (SD) of 93.5% (14.9) in the SMO group and of 91.4% (14.5) in the placebo group (p=0.21). When site and site-by-treatment interaction were included in the model, the point estimate for compliance and the p value were improved in favor of SMO but results did not reach statistical significance.

Safety

The most frequently reported AEs were dizziness and nausea with similar incidence rates in the two groups (Table 3). The number of patients with AEs leading to discontinuation of study medication was lower in SMO group (6 patients) than in the placebo group (11 patients). The most experienced AE leading to discontinuation was nausea with 2 (1.3%) patients in the SMO group and dizziness with 3 (1.9%) patients in the placebo group.

One death was reported in the SMO group: the patient was murdered while consuming alcohol. Five patients in the SMO group experienced non-fatal SAEs compared with six patients in the placebo group. A total of 3 patients experienced SAEs that were considered by the investigator to be related to study medication: one overdose and one suicidal depression (SMO), one drug toxicity (placebo).

No AE related to abuse or misuse were reported. The craving for medication was similar in both treatment groups at Day 180 (SMO group: mean (SE) 38.21 (2.93), placebo group: 37.98 (3.40) on a scale of 1-100) and remained of the same magnitude at follow-up visits without any significant difference between treatment groups. At Day 180, 98.6% of patients in the SMO and 96.6% of patients in the placebo group reported having no desire to take study medication or a desire to take study medication more seldom than every 2-3 hours in the last 30 days. At follow-up visits, these proportions remained of the same magnitude as for Day 180 without any significant difference between treatment groups.

Table 3. Treatment Emergent Adverse Events — Safety Population

	SMO (n = 154)	PBO (n = 160)	p-value
AE	29 (18.8)	32 (20.0)	0.79
AE reported by at least 2 patients			
Dizziness	9 (5.8)	8 (5.0)	0.74
Nausea	4 (2.6)	5 (3.1)	0.78
Headache	3 (1.9)	3 (1.9)	0.96
Vomiting	3 (1.9)	2 (1.3)	0.62
Bronchitis	2 (1.3)	0 (0.0)	0.29
Arthralgia	0 (0.0)	2 (1.3)	0.31
Disturbance in attention	0 (0.0)	2 (1.3)	0.31
Somnolence	2 (1.3)	0 (0.0)	0.29
Alcohol withdrawal syndrome	1[a] (0.6)	2[a] (1.3)	0.58
Alcoholism	0 (0.0)	3[b] (1.9)	0.21
Delirium tremens	2[c] (1.3)	0 (0.0)	0.29
Dermatitis	1 (0.6)	1 (0.6)	0.98
SAE	6 (3.9)	6 (3.8)	0.95
AE treatment related	14 (9.1)	11 (6.9)	0.47
SAE treatment related	2 (1.3)	1 (0.6)	0.62
AE leading to discontinuation	6 (3.9)	11 (6.9)	0.24
Fatal AE	1 (0.6)	0 (0.0)	0.49

Data are numbers of patients (%). AE: adverse events; SAE = serious adverse events.
p-value based on Chi-square test except for SAE treatment related and Fatal AE (Fisher exact test).
[a] these events occurred during the treatment period: one was considered serious (placebo group), one related to study medication (placebo group), and one not serious and not related to study medication (SMO group)
[b] craving for or relapse to alcohol (with hospitalization in one case)
[c] none were considered to be serious or to be related to study medication. These events occurred during the follow-up (e.g. untreated) period (one at day 224 and one at day 291)

DISCUSSION

SMO has previously shown efficacy in the MoA in short-term RCTs (Caputo et al., 2007, 2003; Gallimberti et al., 1992; Guiraud et al., 2021; Leone et al., 2010; van den Brink et al., 2018). The current double-blind placebo controlled RCT confirmed these findings showing a statistically significant and clinically relevant effect of SMO in the pre-specified fixed-effect model of the primary endpoint, CAD during 6 months treatment with a mean difference of +43 days. In addition, the effect of SMO in terms of CAD was still present at the end of the 12-month observation period.

The estimated treatment effect across sites varied from -16 days to +130 days of CAD and a potential site-by-treatment interaction was identified, suggesting heterogeneity of treatment effect. To provide a statistical basis for the generalization of the intervention results to the total AD population from which

the sites were randomly selected, site-level random effect meta-analyses were applied. Results showed point estimates of the treatment effect consistent with those from the fixed effect two-way ANOVA and indicated an important heterogeneity of treatment effect across sites.

Heterogeneity of the SMO effect in the MoA has also been observed in previous SMO RCTs with a larger effect size in patient populations with a lower placebo response rate (Guiraud et al., 2021; van den Brink et al., 2018). This heterogeneity in efficacy is not specific to the treatment of AD with SMO. In a meta-analysis of 51 RCTs for AD, the variability of the effect sizes of acamprosate and naltrexone across trials was substantial and the treatment effect estimates were significantly negatively correlated with the placebo response in the study population (Litten et al., 2013). In the current trial, the placebo response in terms of CAD (mean 73 days at study level) was higher than expected (40-50 days) and the treatment effect was negatively correlated with the placebo response at site level: the lower the placebo response, the higher the treatment effect in the site. Although this post-hoc finding should be interpreted with caution, it is important to further study moderators of SMO treatment effect and the predictors of the placebo response. For example, recent subgroup analyses of RCTs and a meta-regression of 19 RCTs found higher placebo responses in AD patients with more than 14 consecutive days of abstinence prior to randomization (Gueorguieva et al., 2012, 2011; Scherrer et al., 2021; van den Brink et al., 2018). In the GATE 2 study, only patients with a detoxification period of at least 20 days were included and this may explain the relatively high placebo response at study level. There is a convergence of evidence that the duration of abstinence before treatment initiation and/or the baseline alcohol consumption could be moderators of the effect of SMO in AD (Guiraud et al., 2021; Scherrer et al., 2021; van den Brink et al., 2018). Unfortunately, these baseline data were not collected in current study. 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). Interestingly, SMO has previously shown efficacy with large effect sizes in treatment-resistant AD patients (Maremmani et al., 2001) and also in RCTs conducted in high-severity population, i.e., in patient populations with a low response rate to placebo (van den Brink et al., 2018). Consequently, in Italy, SMO was approved for the MoA in treatment-resistant AD patients only.

The current study also showed a sustained effect of SMO on CAD 6 months after study medication discontinuation. The treatment effect in CAD was higher at the end of the study period than at the end of the treatment period and was clinically relevant. The duration of the follow-up period in trials in the treatment of AD is still debated among the scientific community and regulatory agencies. Based on

data indicating that abstinence at 6 months has been shown to be a predictor of long-term abstinence, the US Food and Drug Administration (2015) does not require any specified follow-up period in confirmatory trials for AD. On the other hand, some researchers considered that post-treatment evaluations had to include at least 12 weeks of observation (Rösner et al., 2010b) whereas the European Medicines Agency recommends a follow up of 12-15 months (European Medicines Agency, 2010).

CAD is no longer the primary endpoint recommended by European guidelines for studies on MoA. However, CAD measures the differences in CAR, the current primary endpoint recommended by European guidelines. In GATE 2, the statistically significant beneficial effect of SMO in CAD is explained by a numerically higher CAR and a longer abstinence duration in relapsing patients.

The dropout rates in the current study were high but 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). In addition, drop-outs were considered as drinking days/failures in the CAD and the CAR. Moreover, a sensitivity analysis on the primary endpoint using multiple imputation and a fixed-effect model supported the results of the pre-specified analysis of the primary endpoint. Unfortunately, the estimated Tau^2 was negative in the site-level random effect meta-analysis, indicating that this sensitivity analysis was not possible with this type of analysis and this data set.

No difference between treatment groups was found in GGT and MCV at end of treatment. However, GGT and MCV values were almost normal at baseline, possibly due to the long detoxification period (20 days), which left limited room for improvement during the treatment phase.

The 11 study sites were opened almost on a sequential basis with a mean recruitment duration of 1.5 years/site, explaining the recruitment duration of 10 years. However, randomization was stratified by site and the sponsor, investigators, and patients remained blind for the treatment allocation during the full 12-month study period and unblinding took place only after the last patients of the last site completed the study. Therefore, we believe that neither the external nor the internal validity of the study was jeopardized. Only 6 patients were assessed for eligibility and excluded from the study. This is mainly explained by the fact that the GATE 2 study was conducted concomitantly and at the same sites as the GATE 1 RCT, which tested the equivalence of SMO and oxazepam for treating the alcohol withdrawal syndrome and in which 454 subjects were screened and 128 were randomized (Caputo et al., 2014). As they were fulfilling GATE 2 inclusion criteria, participants who were successfully detoxified with either SMO or oxazepam and who completed the 20-day study period in the

GATE 1 trial were invited to participate in the GATE 2 study. Since patients and investigators remained blind to treatment assignment during the study period in both GATE 1 and GATE 2, we do not expect any serious risk of bias in the GATE 2 findings resulting from the recruitment of patients detoxified with SMO. In addition and since criteria for participation were more stringent in GATE 1, patients who were fulfilling GATE 2 inclusion criteria but who were excluded from the GATE 1 study, for instance due to the lack of moderate or severe alcohol withdrawal syndrome, were also invited to participate in the GATE 2 study.

The adverse event profile was as expected from previously published data from pharmacovigilance and clinical studies (Addolorato et al., 2020) and reflects the pharmacological profile of SMO. No significant group differences were found in the incidence of AEs. The most reported AEs were effects on the nervous system (dizziness) and gastrointestinal apparatus (nausea). No difference in craving for study medication was detected between treatment groups, suggesting a low risk of abuse and dependence to SMO in the study population. One death (murdered) was reported but was not considered to be related to the study medication. Overall, SMO was well-tolerated.

In conclusion, SMO showed efficacy in CAD during the 6-month treatment period in this double-blind RCT. The current RCT confirms efficacy and safety of SMO in the treatment of AD reported in previous RCTs and pharmacovigilance database, especially for patient populations with a low placebo response rate. In this subgroup of severe AD patients, additional data are warranted to further support the clinically relevant effect of SMO.

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Giovanni Addolorato served as a consultant for Ortho-McNeil Janssen Scientific Affairs, LLC, and D&A Pharma, and was paid for his consulting services. He has received lecture fees from D&A Pharma.

Henri-Jean Aubin reports being member of advisory boards or DSMB for Bioprojet, and Ethypharm, and has received sponsorship to attend scientific meetings, speaker honoraria or consultancy fees from Bioprojet, D&A Pharma, Ethypharm, Kinnov Pharmaceuticals and Lundbeck. He is also member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative (ACTIVE), which was supported in the last three years by Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Indivior, Lundbeck, Mitsubishi, and Otsuka.

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Icro Maremmani served as board member for Angelini, Camurus, CT Sanremo, D&A Pharma, Gilead, Indivior, Lundbeck, Molteni, MSD, Mundipharma.

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Roberto Cacciaglia is employed by Laboratorio Farmaceutico CT, San Remo, Italy. Julien Guiraud is employed by D&A Pharma, Paris, France. Roch Poulnais and Quentin Raffaillac were employed by D&A Pharma, Paris, France. None of the other authors received financial support for the current work.

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CHAPTER 4

Baseline severity and the prediction of placebo response in clinical trials for alcohol dependence: a meta-regression analysis to develop an enrichment strategy

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ABSTRACT

Background: There is considerable unexplained variability in alcohol abstinence rates (AR) in the placebo groups of randomized controlled trials (RCTs) for alcohol dependence (AD). This is of particular interest because placebo responses correlate negatively with treatment effect size. Recent evidence suggests that the placebo response is lower in very heavy drinkers who show no "spontaneous improvement" prior to treatment initiation (high-severity population) than in a mild-severity population and in studies with longer treatment duration. We systematically investigated the relationship between population severity, treatment duration, and the placebo response in AR to inform a strategy aimed at reducing the placebo response and thereby increasing assay sensitivity in RCTs for AD.

Methods: We conducted a systematic literature review on placebo-controlled RCTs for AD. We assigned retained RCTs to high- or mild-severity groups of studies based on baseline drinking risk levels and abstinence duration before treatment initiation. We tested the effects of population severity and treatment duration on the placebo response in AR using meta-regression analysis.

Results: Among the 19 retained RCTs (comprising 1996 placebo-treated patients), 11 trials were high-severity and 8 were mild-severity RCTs. The between-study variability in AR was lower in the high-severity than in the mild-severity studies (interquartile range: 7.4% vs. 20.9%). The AR in placebo groups was dependent on population severity ($p = 0.004$) and treatment duration ($p = 0.017$) and was lower in the high-severity studies (16.8% at 3 months) than the mild-severity studies (36.7% at 3 months).

Conclusions: Pharmacological RCTs for AD should select high-severity patients to decrease the magnitude and variability in the placebo effect and improve the efficiency of drug development efforts for AD.

INTRODUCTION

Alcohol dependence (AD) affects 7.7% and 3.4% of the adult population in the United States of America and in the European Union, respectively (Rehm et al., 2015; World Health Organization, 2018) and accounts for 71% of all alcohol-related harm and for 60% of all social costs related to alcohol (Rehm et al., 2013). There is strong evidence that alcohol-related harm is determined by the amount of alcohol consumed and the specific drinking pattern (Rehm et al., 2010). The amount of alcohol consumption has been categorized in different Drinking Risk Levels (DRLs) by the World Health Organization (WHO) (World Health Organization, 2000) and subjects with a Very High (VH) DRL (see Table S1) are responsible for the majority of AD attributable burden (Hasin et al., 2017; Rehm et al., 2018). Therefore, subjects with a VH-DRL constitute a target population of primary concern in the treatment of AD.

One of the AD treatment objectives is the achievement of stable abstinence by prevention of relapse after detoxification (European Medicines Agency, 2010). Approved treatments in the maintenance of alcohol abstinence in the United States of America and in Europe include acamprosate, naltrexone and disulfiram. In addition, nalmefene has been approved by the European Medicines Agency (EMA) for the reduction of alcohol consumption. However, these proven-effective medicines only show modest efficacy with many patients not responding to these treatments (European Medicines Agency, 2010; Litten et al., 2012; van den Brink et al., 2018) and thus there is a need for additional treatments. However, development of medications for the treatment of AD is challenging and the demonstration of efficacy of treatments approved for this indication is based on a mix of positive and negative studies (European Medicines Agency, 2010; Litten et al., 2012; Witkiewitz et al., 2019). One of the main reasons for these mixed results has been the unpredictable variability of the placebo response in RCTs for AD. In an analysis on 51 naltrexone and acamprosate double-blind RCTs, the placebo response was significantly negatively correlated with the treatment effect size on total abstinence (Litten et al., 2013). It is recognized that studies often fail when the placebo response is high (European Medicines Agency, 2007). In this context, the development of enrichment strategies for clinical trials for AD will increase the reliability of the expected effect size thanks to decrease of variability of the placebo response and increase the power of the study thanks to decrease of the placebo effect. It will therefore improve the efficiency of drug development through targeting the treatment to those patients who will benefit the most from pharmacological interventions. Enrichment is the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if in fact present) is

more likely than it would be in an unselected population (US Food and Drug Administration, 2019).

Numerous factors potentially predicting placebo response in the treatment of AD have been studied over the last 20 years such as study design and demographic characteristics (Litten et al., 2013). Recent subgroup analyses in studies for the treatment of AD suggest that the placebo response in double-blind RCTs is higher and treatment effect size is lower in patients with a Low or Medium DRL at baseline (L/M DRL: see Table S1), in patients with more than 14 consecutive days of abstinence before treatment initiation ('early abstainers'), and/or in patients who reduce their alcohol consumption to a L/M DRL prior to treatment initiation ('early reducers'). Conversely, placebo response is lower and treatment effect size is higher in the complement population which includes AD patients with a High or VH DRL at baseline (H/VH DRL, see Table S1) and who are not early abstainers/reducers (Gual et al., 2013; Gueorguieva et al., 2012, 2011; Mann et al., 2016; van den Brink et al., 2018, 2014, 2013). In other words, and in analyses at patient level, the placebo response seems to be lower and treatment effect size higher in heavy drinkers without spontaneous improvement before treatment initiation. With respect to their level of response to placebo treatment, not early abstainers/reducers with H/VH DRL have been defined in the literature as the high-severity AD population and L/M DRL or early abstainers/reducers as the mild-severity AD population (van den Brink et al., 2018). Although the effect of this notion of AD severity has been studied at patient level, it has so far not been systematically investigated at study level. In addition, analyses at patient level showed that 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). However, in a previous meta-analysis of 51 RCTs for AD, the placebo response at study level was not dependent on the unadjusted treatment duration (Litten et al., 2013). Nevertheless, the effect of treatment duration on the placebo response has so far not been adjusted for population severity at study level.

Therefore, the current study systematically and simultaneously investigated the relationships of the placebo response in the maintenance of abstinence in double-blind RCTs with population severity (high versus mild-severity) and treatment duration to explore whether an enrichment strategy using these potential predictors might help to reduce the variability of the placebo response and increase assay sensitivity in future clinical trials.

MATERIALS AND METHODS

Study selection and systematic review

A systematic literature review was performed to select double-blind placebo controlled RCTs investigating the efficacy of approved pharmacological interventions, new chemical entities or repurposed medications in the maintenance of abstinence in alcohol dependent patients and conducted with similar experimental conditions (except for the population severity and the treatment duration).

The Miller et al. (Miller et al., 2011) systematic literature review on medical treatment of AD was screened to obtain keywords for pharmacological substances or repurposed medications tested in the treatment of AD. They were reviewed and expanded based on authors' knowledge and were then used for a systematic literature search by the online portal of the National Library of Medicine (https://pubmed.ncbi.nlm.nih.gov/) including PubMed, PubMed Central, and MEDLINE. A systematic screening of the original articles published until October 1, 2020 was performed based on PRISMA guidelines and the keywords and combinations are provided in the supplementary methods. In addition, the reference sections of identified papers as well as review and meta-analysis articles were screened for further relevant citations. Three reviewers (JG, RP and QR) independently screened titles and abstracts of articles and read the full text of papers deemed potentially eligible by either reviewer. Reviewer disagreements were solved by discussion and consensus was reached in all instances. Only peer-reviewed original articles written in English were retained if they fulfilled inclusion/non-inclusion criteria.

Only comparative, parallel arms, double-blind, randomized, placebo-controlled (oral) medication trials conducted to maintain abstinence from alcohol were eligible. Included studies enrolled alcohol dependent patients as diagnosed with DSM (IV or earlier), ICD (10 or earlier) or equivalent criteria. Studies enrolling patients with co-occurring disorders (severe psychiatric comorbidities, polydrug or other substance use disorders (except tobacco) or severe hepatic dysfunction (liver cirrhosis, HCV)) were excluded. Patients had to be abstinent before starting the study medication and to be monitored in an outpatient setting during the treatment phase.

Only studies reporting the abstinence rate were included. Abstinence rate is the primary endpoint recommended by the US Food Drug Administration (FDA) and the European Medicines Agency (EMA) for demonstration of efficacy in the maintenance of abstinence (European Medicines Agency, 2010; US Food and Drug Administration, 2015). Our definition of abstinence was continuous

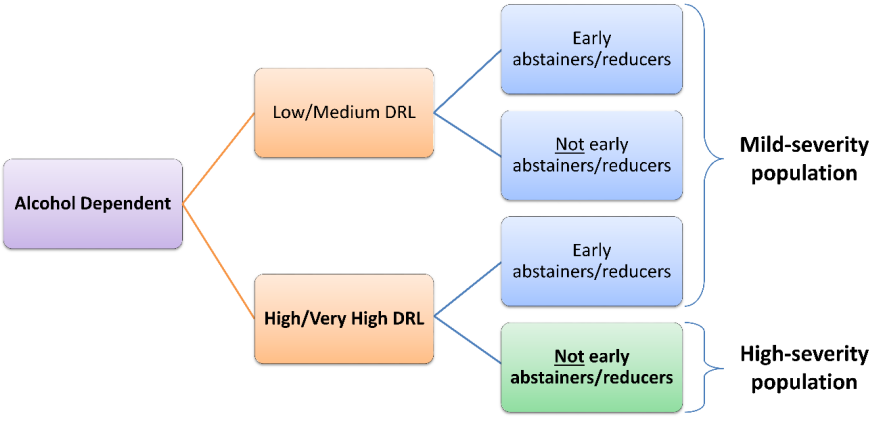
abstinence (no relapse to any alcohol use) throughout the treatment period. Studies with other outcome definitions were excluded. Dropouts were treated as treatment failures (patient not continuously abstinent). The following information was extracted in duplicate using a data collection form, which has been piloted, from each retained study: 1) treatment duration, 2) alcohol consumption prior to screening in the placebo arm, 3) abstinence duration before randomization, 4) total number of patients allocated to the placebo arm, 5) total number of continuously abstinent patients in the placebo arm at end of treatment and 6) any other reported baseline characteristics. Data from the retained studies were then used to assign studies to the group of high-severity or the group of mild-severity studies.

Allocation of studies in each population

Assignment of studies to the group of high-severity or the group of mild-severity studies was based on the two criteria defined in the literature for trials directed at maintenance of abstinence: level of alcohol consumption at baseline and abstinence duration before treatment initiation.

The first criterion is based on WHO DRL to categorize patients depending on their mean alcohol consumption (in grams of pure alcohol per day) at baseline (Figure 1, Table S1). If the reported mean alcohol consumption at baseline in the placebo group was lower than the Medium DRL threshold (60 g alcohol/day for men and 40 g alcohol/day for women), the study was considered as being conducted in the L/M DRL population. If only the mean number of standard drinks at baseline in the placebo group was reported, then the conversion to grams was performed using the following country-specific standard drinking units: South Korea 8g; Australia, Belgium, France 10g; Italy 12 g; United States of America 14 g; Germany 15 g (World Health Organization, 2018). RCTs conducted in L/M DRL populations were allocated to the mild-severity population regardless of the abstinence duration prior to treatment (Figure 1).

Figure 1. Definitions of alcohol-dependent subpopulations according to van den Brink et al. (2018)



For RCTs not categorized as L/M DRL studies, a second criterion linked to the abstinence duration before treatment initiation was applied, which allowed to distinguish not early abstainers from other patients (Figure 1). If the inclusion/exclusion criteria specified a detoxification period of less than 14 days prior to treatment initiation, the study was considered to be conducted in not early abstainers. Conversely, studies with inclusion/exclusion criteria specifying a detoxification period longer than 14 days were considered to be conducted in early abstainers. The mean detoxification or pretreatment abstinence duration was used in case it was not possible to classify the study based on the inclusion/exclusion criteria. Studies with a mean detoxification or pretreatment abstinence duration ≤ 11 days were considered as being conducted in not early abstainers. Conversely, studies with a mean detoxification or pretreatment abstinence duration ≥ 17 days were considered as conducted in early abstainers. Studies with a mean detoxification or pretreatment abstinence period between 11 and 17 days were excluded as it was too close from the 14 days threshold and thus, we considered that they were conducted in both early and not early abstainers and that they cannot be allocated to any population severity group.

Studies that were considered as conducted in not early abstainers with H/VH DRL were assigned to the group of high-severity studies and studies considered as conducted in early abstainers or in L/M DRL patients were assigned to the group of mild-severity studies (Figure 1).

Because mean values of alcohol consumption and detoxification duration were used to assign studies, it can be argued that these studies may have included a mix of both mild-severity and high-severity patients. To address this point, a

sensitivity analysis has been performed: the dichotomous population severity factor in the main analysis (mild-severity vs. high-severity studies) was replaced by the percentage of high-severity patients as a continuous variable. The percentage of high-severity patients assuming independence of both criteria was determined for each study retained by multiplying the percentage of not early abstainers by the percentage of H/VH DRL patients. For instance, for a study with a percentage of not early abstainers of 80% and a percentage of H/VH DRL patients of 70% in the placebo group, the percentage of high-severity patients is 56% (=80%*70%). The percentage of not early abstainers and of H/VH DRL patients were computed based on the reported mean detoxification duration and mean alcohol consumption in placebo group, respectively and their related standard deviation and assuming a normal distribution. To assess the possible effect of the probability density function, a further sensitivity analysis using a lognormal distribution of alcohol use and abstinence duration was performed. Additional information on the above methods is available in the supplementary material.

Since studies with a mean abstinence duration before treatment initiation between 11 and 17 days were excluded from the sample used in the primary analysis, a sensitivity analysis was conducted adding these studies to the analysed sample of RCTs (“extended sample”) and investigating the effect of the percentage of high-severity patients and treatment duration on the placebo response in abstinence rate.

The risk of bias assessment for RCTs in this review was performed using the criteria recommended by the Cochrane Handbook (Higgins et al., 2020): sequence generation; allocation concealment; completeness of outcome data; selective reporting; other possible bias, such as similarity of patients in the groups; blinding of patients, providers and of subjective outcomes (more information is provided in supplementary methods).

Statistical analyses

The primary outcome for this study was the abstinence rate. The effect of the potential predictors of the abstinence rate in the placebo groups was analysed by hierarchical multiple meta-regressions on study level (Harrer et al., 2019, Higgins et al., 2020).

In the main analysis, the two covariates associated with placebo response differences in previous research were included into the meta-regression model: 1) the dichotomous subpopulation variable as defined above (mild-severity versus high-severity), and 2) the intended duration of treatment. In the sensitivity analyses, the two covariates included in the meta-regression model were: the

continuous variable defining the percentage of high-severity patients and the intended duration of treatment.

A secondary meta-regression analysis was conducted including the two original explanatory variables (subpopulation and treatment duration) and a new set of independent variables composed of any other baseline patient characteristics reported in retained studies to adjust the effect of factors of interest for potential confounding factors. In order to have enough data for the meta-regression to be sensitive, only baseline characteristics reported in at least 10 studies were retained for this analysis (Borenstein et al., 2010, Higgins et al., 2020).

The effects of (1) mean alcohol consumption at baseline (in g/day) and treatment duration, (2) mean abstinence duration before treatment initiation (in days) and treatment duration, and (3) mean alcohol consumption at baseline, mean abstinence duration before treatment initiation and treatment duration on the abstinence rate were also investigated as secondary analyses.

Statistical significance was set at $p < 0.05$. The principal statistical software used was STATA 14 (StataCorp, 2015).

RESULTS

Study selection and main characteristics of study populations

In total 431 articles were screened, 44 fulfilled the selection criteria and 387 were excluded. The main reasons for exclusion were the following: maintenance of abstinence not the treatment goal (n=137) and re-analysis of already included studies or meta-analyses (n=80) (Figure 2). A list of screened studies and reasons for exclusion is provided in the Supplementary Table S5. Out of the 44 studies that fulfilled all selection criteria, 25 were excluded from the analyses because the reported data did not allow assignment of the study to one of the two pre-defined RCT groups (articles did not report data for each population or data to determine in which population the study was conducted). Among these 25 studies, one reported a mean abstinence duration between 11 and 17 days before treatment initiation (Müller et al., 2015). As a result, 19 RCTs, with 1,996 placebo-treated patients, were assigned to one of the two pre-defined RCT groups and were thus included in the analyses (see list in Table S4).

The mild-severity population group consisted of 8 studies totalling 920 placebo treated patients. The high-severity population group consisted of 11 studies totalling 1,076 placebo treated patients.

Figure 2. Flow diagram of study selection

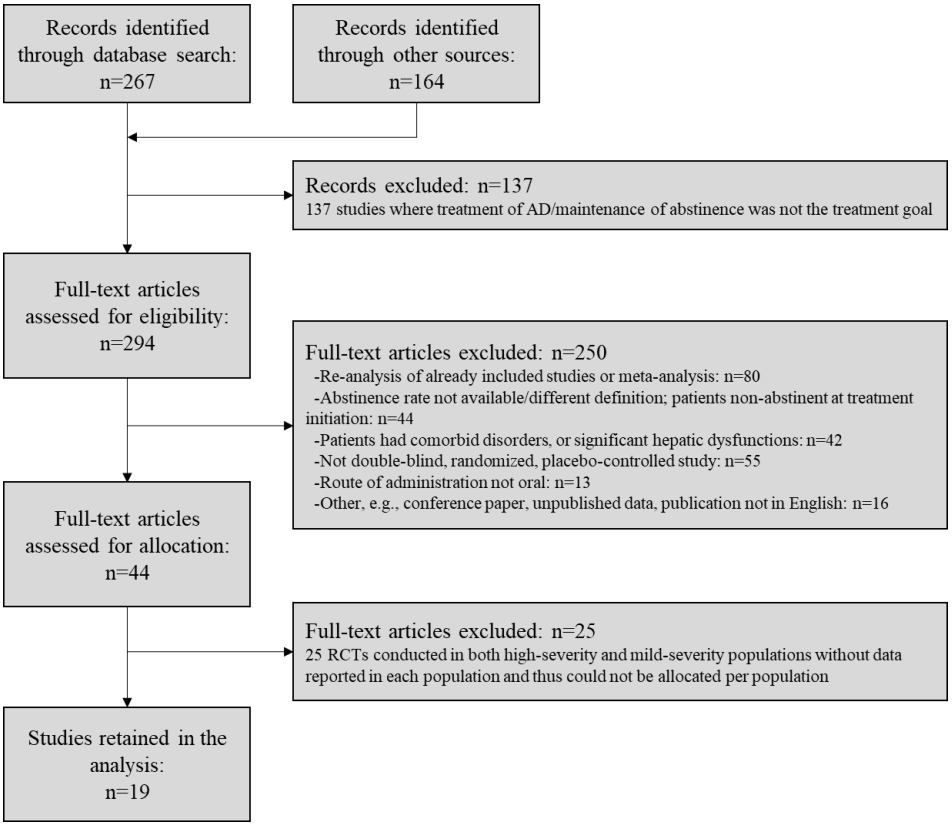


Table 1 shows the main study population characteristics. Mean age at baseline and the percentage of men were reported in 19 and 18 studies, respectively and were similar in the two subpopulations. Other baseline characteristics such as mean Alcohol Dependence Scale (Skinner and Horn, 1984) scores were available in less than 10 studies and were thus not included as independent variables in the meta-regression analysis.

The mean (min, max) percentage of high-severity patients in placebo group was 81% (61%, 100%) in the group of studies assigned to the high-severity population and 13% (0%, 41%) in the group of studies assigned to the mild-severity population, indicating that the assignment of RCTs to each population allowed to distinguish RCTs mainly or exclusively conducted in high-severity patients from RCTs mainly or exclusively conducted in mild-severity population. The overall percentage of H/VH DRL patients and the mean alcohol consumption at baseline was high and paradoxically slightly larger in the mild population indicating that all retained RCTs included mainly H/VH DRL patients who were either severe (not early abstainers) or mild (early abstainers). Thus, the assignment of studies to the mild-severity versus the high-severity group was mainly driven by the abstinence duration before treatment initiation. The mean percentage of not early abstainers was 15% in the group of mild-severity studies and 97% in the high-severity studies (Table 1). The mean (min, max) treatment duration was 3.2 (1.0, 6.0) months in the group of studies assigned to the high-severity population and 6.9 (3.0, 12.0) months in the group of studies assigned to the mild-severity population.

Table 1. Descriptive statistics and main characteristics of placebo groups in retained studies

Characteristics	Statistical parameters	Overall	Mild-severity population	High-severity population
Retained studies	N studies	19	8	11
Sample size	N patients total	1 996	920	1 076
	Mean (SD)	105.1 (84.6)	115.0 (53.4)	97.8 (103.7)
	Min; Max	8; 392	8; 177	19; 392
Treatment duration (in months)	Mean* (SD)	4.7 (3.0)	6.9 (3.4)	3.2 (1.3)
	Min; Max	1.0; 12.0	3.0; 12.0	1.0; 6.0
	Median	4.0	6.0	3.0
	1st and 3rd quartile	3.0; 6.0	5.5; 7.5	3.0; 3.5
Mean age of patients (in years)	Mean* (SD)	45.0 (3.3)	44.4 (4.0)	45.4 (2.9)
	Min; Max	40.5; 53.1	40.5; 53.1	40.6; 49.8

Characteristics	Statistical parameters	Overall	Mild-severity population	High-severity population
	Median	44.3	43.4	44.3
	1st and 3rd quartile	42.5; 46.9	41.9; 45.2	43.6; 47.5
% of male	Mean* (SD)	78.5 (13.9)	78.7 (6.0)	78.4 (18.3)
	Min; Max	42.9; 100	67.8; 88.4	42.9; 100
	Median	78.4	78.7	78.4
	1st and 3rd quartile	70.8; 87.1	76.5; 80.9	67.6; 94.0
Mean alcohol consumption at baseline (in g/day)	Mean* (SD)	136.4 (59.7)	155.0 (43.9)	130.8 (64.5)
	Min; Max	75.7; 288.4	106.5; 192	75.7; 288.4
	Median	120.5	166.5	113.1
	1st and 3rd quartile	94.6; 166.5	136.5; 179.3	92.7; 128.6
Mean abstinence duration before treatment (in days)	Mean* (SD)	15.4 (15.6)	28.3 (16.4)	5.7 (3.3)
	Min; Max	1.0; 60.0	17.2; 60.0	1.0; 11.0
	Median	10.0	22.8	5.3
	1st and 3rd quartile	4.9; 18.9	17.8; 29.0	3.7; 7.5
% of H/VH DRL [1]	Mean* (SD)	83.8 (10.9)	89.4 (9.8)	81.2 (10.9)
	Min; Max	63.8; 100.0	74.0; 100.0	63.8; 100.0
	Median	83.7	89.6	82.0
	1st and 3rd quartile	77.6; 90.6	88.3; 95.0	74.6; 87.3
% of not early abstainers [2]	Mean* (SD)	63.5 (43.7)	15.0 (19.2)	97.3 (6.3)
	Min; Max	0.0; 100.0	0.0; 42.8	79.8; 100.0
	Median	95	0.0	100
	1st and 3rd quartile	27.9; 100	0.0; 31.3	99.6; 100.0
% of high severity patients [3]	Mean* (SD)	52.8 (37.0)	13.2 (17.4)	80.6 (12.2)
	Min; Max	0.0; 100.0	0.0; 40.6	60.6; 100.0
	Median	65.4	0.0	82.6
	1st and 3rd quartile	20.6; 83.2	0.0; 25.8	72.4; 88.7
Abstinence rate (in %)	Mean* (SD)	22.0 (13.2)	29.1 (16.0)	16.8 (8.1)
	Min; Max	4.1; 50.6	9.7; 50.6	4.1; 31.4
	Median	18.8	27.3	16.1
	1st and 3rd quartile	12.9; 29.6	18.6; 39.5	12.5; 19.9

*Unweighted estimate; [1] based on reported mean alcohol consumption values at baseline and related standard deviations and assuming a normal distribution; [2] based on inclusion/exclusion criteria or reported mean detoxification period duration values and related standard deviations and assuming a normal distribution; [3] determined by applying the % of not early abstainers to the % of H/VH DRL patients

Results of the bias evaluation showed a low risk of bias in almost all studies for blinding of participants and personnel, incomplete outcome data, selective reporting, and other types of bias. All studies were randomized and the risk regarding the random sequence generation was judged to be low in 9 RCTs and unclear in the remaining studies. The risk on allocation concealment was judged unclear for most of studies.

Additional information on baseline characteristics and the risk of bias assessment is available in supplementary material.

Relationship of population severity and treatment duration with abstinence rate

Descriptive statistics show that the abstinence rate (16.8% versus 29.1%) and between study variability in abstinence (interquartile range: 7.4% versus 20.9%) are lower in the high-severity than in the mild-severity studies (Table 1).

In the primary meta-regression analysis, the effects of both population severity and treatment duration were significant (p=0.004 and p=0.017, respectively), indicating that the placebo response in abstinence rate was significantly dependent upon population severity and treatment duration (Table 2).

For a 3-month treatment duration, the predicted value of the placebo response in abstinence rate was 16.8% in the high-severity population and 36.7% in the mild-severity population: a significant and clinically relevant difference of 19.9% (Table 3). Likewise, the predicted value of the placebo response in abstinence rate was 9.0% in the high-severity population and 28.9% in the mild-severity population for a 6-month treatment duration (Table 3). After adjustment for population severity, the placebo response in abstinence rate decreased by 2.6 percent per month of treatment, e.g., the longer the treatment duration, the lower the placebo response (Figure 3; Supplementary Table 3). The adjusted coefficient of determination (R^2) was 0.39.

In the sensitivity analyses, the effects of the percentage of high-severity patients and of treatment duration factors were also statistically significant with similar p values but with a higher percentage of variance explained than in the main analysis and with no relevant difference in variance explained between the model assuming normal and lognormal distributions of alcohol use and abstinence duration: adjusted R^2=0.53 assuming normal distributions and adjusted R^2=0.58 assuming lognormal distributions. Similar estimates and p values of the effects of the percentage of high-severity patients and of treatment duration factors were observed when the study with a mean abstinence duration between 11 and 17 days before treatment initiation was included in the sample analysed in the meta-regression model (Table 2; Table S3).

Table 2. Results of meta-regression models with abstinence rate as the dependent outcome

Analysis		Terms	Estimate	p value	Adjusted* R^2	Heterogeneity
Primary Analysis						
Main analysis		Tx Duration Pop. severity	-0.0256 -0.1987	p=0.017 p=0.004	$R^2_{adj.}$ = 0.39	I^2=0.84 tau²=0.007
Sensitivity analysis: % of high-severity patients	Normal distribution	Tx Duration % Severe	-0.0252 -0.3153	p=0.013 p=0.001	$R^2_{adj.}$ = 0.53	I^2=0.82 tau²=0.007
	Log-normal distribution	Tx Duration % Severe	-0.0236 -0.3023	p=0.012 p=0.001	$R^2_{adj.}$ = 0.58	I^2=0.80 tau²=0.006
	Extended set of studies[1]	Tx Duration % Severe	-0.0249 -0.3150	p=0.012 p=0.001	$R^2_{adj.}$ = 0.53	I^2=0.81 tau²=0.006
Secondary Analyses						
Age and % of males		Tx Duration Pop. severity Age % Male	-0.0265 -0.1978 -0.0000 0.1643	p=0.027 p=0.008 p=0.998 p=0.368	$R^2_{adj.}$ = 0.32	I^2=0.86 tau²=0.009
Alcohol consumption at baseline		Tx Duration Consumption	-0.0162 0.0004	p=0.280 p=0.534	$R^2_{adj.}$ = -0.06	I^2=0.88 tau²=0.014
Abstinence duration before treatment initiation		Tx Duration Abs Duration	-0.0207 0.0054	p=0.138 p=0.041	$R^2_{adj.}$ = 0.26	I^2=0.85 tau²=0.011
Abstinence duration and alcohol consumption		Tx Duration Abs Duration Consumption	-0.0377 0.0194 0.0005	p=0.051 p=0.044 p=0.440	$R^2_{adj.}$ = 0.39	I^2=0.84 tau²=0.010

*: The adjusted R^2 adjusts for the number of terms in the model.
[1]: assuming a normal distribution. The extended set of studies included 20 RCTs: the 19 studies retained in the main analysis and the study with a mean abstinence duration before treatment initiation between 11 and 17 days: Müller et al., 2015. The percentage of high-severity patient in this study was estimated at 61%, the retained treatment duration was 4 months, the reported abstinence rate was 14.3% and the placebo group included 28 patients.
Tx: treatment; Pop: population; Abs Duration: mean abstinence duration before treatment initiation; Consumption: mean alcohol consumption at baseline

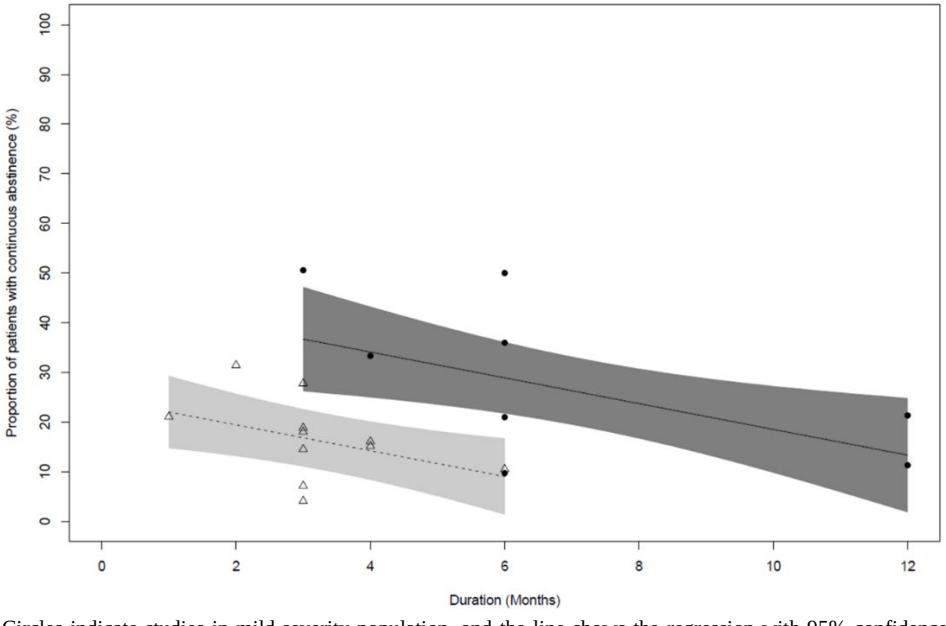
In the secondary analysis with the mean age at baseline and the percentage of males included in the meta-regression analysis, results showed no significant effect of these factors on the placebo response whereas the effect of population severity and of treatment duration remained significant (p=0.008 and p=0.027, respectively). The mean alcohol consumption at baseline adjusted for treatment duration was not a significant predictor of the placebo response (p=0.534), whereas the mean abstinence duration before treatment initiation adjusted for treatment duration had a significant effect on the placebo response (p=0.041). However, the variance explained by this model (adjusted R^2=0.26) was lower than in the primary analysis. In the model with the mean abstinence duration before treatment initiation, the mean alcohol consumption at baseline, and treatment duration as independent variables, only the abstinence duration before treatment initiation showed a significant effect on the placebo response (p=0.044), but the variance explained by this model was similar to the primary analysis (adjusted R^2=0.39) (see Table 2 and Table S3).

Table 3. Predicted values (95% C.I.) of the placebo response in abstinence rate

Predicted values	**Month 3**	**Month 6**
Mild-severity population		
Main analysis	36.7% (26.2; 47.2)	28.9% (21.7; 36.1)
Sensitivity analysis – normal distribution[1]	42.1% (30.4; 53.8)	34.5% (25.7; 43.4)
Sensitivity analysis – log-normal distribution[1]	42.3% (31.3; 53.4)	35.3% (26.7; 43.9)
High-severity population		
Main analysis	16.8% (11.1; 22.6)	9.0% (1.4; 16.7)
Sensitivity analysis – normal distribution[2]	10.6% (3.2; 18.0)	3.0% (-6.4; 12.4)
Sensitivity analysis – log-normal distribution[2]	12.1% (5.7; 18.6)	5.0% (-2.9; 13.0)

[1]: Predicted estimates for a % of high-severity patients of 0%
[2]: Predicted estimates for a % of high-severity patients of 100%

Figure 3. Relationship between abstinence rate and treatment duration in high-severity population and mild-severity population (meta-regression)



Circles indicate studies in mild-severity population, and the line shows the regression with 95% confidence band. The triangles show studies in high-severity population and the dotted line shows the regression with 95% confidence band

DISCUSSION

The effect size of pharmacological interventions for the treatment of AD is generally rather modest and is negatively correlated with the placebo response rate in RCTs (Jonas et al., 2014; Litten et al., 2013). However, understanding the nature of the placebo effect in RCTs for AD remains poor and a better characterization of factors that predict placebo response is warranted. Indeed, placebo effects are powerful and common in neuropsychiatric disorders and in clinical practice in general (Colloca and Barsky, 2020).

Here we studied population severity and treatment duration as two potential drivers of the placebo response in these studies. The population severity is categorical variable with two categories which have been defined in literature with respect to their effect on placebo response and treatment effect. It distinguishes heavy drinkers without "spontaneous improvement" prior to treatment initiation (high-severity) from other patients (mild-severity) (van den Brink et al., 2018).

In our meta-regression analysis of 19 RCTs with 1,996 placebo-treated AD patients, placebo response in abstinence rate was significantly lower in the high-severity studies than in the mild-severity studies. The significant decrease by 19.9% in points for the placebo response in abstinence rate in the high-severity compared to the low-severity studies is clinically meaningful. These results are in line with previous subgroup analyses of single RCTs for AD where early abstainers/reducers and L/M DRL patients showed a higher placebo response (and a lower treatment effect) than H/VH DRL patients not early abstainer/reducers (Gual et al., 2013; Gueorguieva et al., 2012, 2011; Mann et al., 2016; van den Brink et al., 2018, 2014, 2013). In addition, 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).

These findings were supported in the current meta-regression analysis by results from a sensitivity analysis using the percentage of high-severity patients in the studies as a predictor of placebo response. Moreover, the variance explained was higher in the sensitivity analysis than in the primary analysis. This may be partly explained by the use of a continuous predictive variable which considers that certain studies had a mixed population of mild-severity and high-severity patients. Almost identical results were obtained in the sensitivity analysis using the extended sample which included 20 RCTs: the 19 retained RCTs as well as the Müller et al. (2015) study reporting a mean abstinence duration before treatment initiation between 11 and 17 days. These data indicate that the placebo

response in the Müller et al. (2015) study was consistent with the modelling estimate based on the 19 RCTs, which strengthens the results of the primary analysis. Interestingly, the reported placebo response in abstinence rate in Müller et al. (2015) is 14.3% when the predicted estimates of the placebo response for this study are 20.3% and 16.1% in the models assuming a normal and a log-normal distribution, respectively, and using the main sample of studies (i.e., 19 RCTs). Therefore, and since it also showed the highest variance explained (adjusted R^2=0.58), the model using the percentage of high-severity patients adjusted for treatment duration and assuming a log-normal distribution of the alcohol consumption at baseline and of the abstinence duration pre-treatment may provide better predicted estimates of the placebo response.

In secondary analyses, the placebo response was associated with the mean abstinence duration before treatment initiation but not with the mean alcohol consumption at baseline. In our meta-regression, the population severity effect was mainly driven by the 'early abstainer' factor as opposed to previous subgroup analyses of RCTs where population severity was driven exclusively by baseline DRL (van den Brink et al., 2018) or by both baseline DRL and early abstainer/reducer (Gual et al., 2013; Gueorguieva et al., 2012, 2011; Mann et al., 2016; van den Brink et al., 2014, 2013). This difference in the explanatory power of each factor can be explained as follows: in the current meta-regression analysis, the percentage of early abstainers varied widely, whereas the baseline DRL was very similar across studies (similar percentage of H/VH DRL). Thus, this DRL factor was almost a constant in the present analysis (that cannot explain variance of the response), whereas the early abstainer factor showed a large range of variation (and can explain variance of the response). Consequently, in the current meta-analysis, the population severity effect was mainly driven by the early abstainer factor. In another study, the opposite was the case: big variation in population severity and small or no variation in early abstainers and thus the population severity effect was driven by the baseline DRL factor (van den Brink et al., 2018). Finally, in RCTs where the population severity effect was driven by both baseline DRL and early abstainer/reducer, both factors showed large variation (Gueorguieva et al., 2011, 2012; van den Brink et al., 2013, 2014; Gual et al., 2013). Thus, the contribution of each factor (baseline DRL vs. early abstinence) in the population severity effect on the placebo response appears to be dependent on sample and study design.

The current meta-regression analysis reconciles the seemingly conflicting results related to the effect of treatment duration on abstinence in the placebo group between patient level and study level analyses. At study level and in the current analysis, treatment duration adjusted for population severity was a predictor of the placebo response as consistently shown by others at the patient level in single RCTs (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). However, in a previous meta-analysis of 51 RCTs, the placebo response at study level was not dependent on the unadjusted treatment duration (Litten et al., 2013). In the current meta-regression analysis, the placebo response was also not dependent on treatment duration when the latter was adjusted for the mean alcohol consumption at baseline and/or the mean abstinence duration before treatment initiation. These results suggest that, at study level, treatment duration should be adjusted for population severity to show an effect on abstinence in the placebo group.

The effects of mean age at baseline and percentage of males on the placebo response in abstinence rate were not significant and support prior results for percentage of males in another meta-analysis (Litten et al., 2013). However, in this previous meta-analysis, mean age was associated with the placebo response in the percentage of days abstinent in naltrexone RCTs but not in acamprosate studies (Litten et al., 2013).

Results of our meta-regression also showed a decrease of between-study variability in response rates in the placebo group. Consequently, power calculation of future RCTs should be more reliable because the expected treatment effect is less random. This approach should improve assay sensitivity in the detection of true positive treatment effects (Litten et al., 2012). Nevertheless, the complex nature of the placebo response was not fully explained by population severity and the treatment duration, and other factors must be explored at the patient level to further reduce placebo response variability. Since abstinence was determined using patient's self-reported alcohol consumption, some of the unexplained variance in the placebo response may also be due to the inaccuracy of self-reported measures of alcohol consumption (de Bejczy et al., 2015). In addition, the retained trials may have included some patients for whom the drinking goal was not abstinence (but reduced drinking) which may have had an effect on the placebo response and this mismatch of treatment goals may explain a portion of the residual unexplained variance (Bujarski et al., 2013; DeMartini et al., 2014).

The number of studies conducted in the mild-severity and the high-severity population was rather well-balanced with 8 and 11 studies and about 1,000 patients in each subpopulation. Such balance provides better power to detect the effect of study factors. However, the predicted values for the placebo response are limited by a treatment duration of only 6 months in the enriched (e.g., high-severity) population, because there were no studies with a longer treatment duration that also met all study inclusion criteria.

Results of risk of bias evaluation showed a low or unclear risk of bias for almost all criteria and all studies.

Overall, our results call for the re-evaluation of large trials conducted in unselected study populations and re-analysis of the data considering baseline DRL and abstinence duration prior to treatment. This approach was recently applied to an RCT with sodium oxybate (van den Brink et al., 2018). In the latter study, the abstinence rate in the placebo arm at the end of the 3-month treatment period was 15% in the high-severity population compared to 40% in the mild-severity population which is consistent with our modelling estimates. This post-hoc finding strengthens the conclusions of the current systematic study on the population enrichment strategy. The here proposed enrichment strategy could be practically implemented by enrolling only H/VH DRL patients and by applying a treatment-free run-in period of at least two weeks to exclude patients with a mild disorder and/or spontaneous improvement.

A potential drawback of applying enrichment strategies is a decrease of external validity/generalizability through exclusion of a specific part of the patient population (Leber and Davis, 1998). However, the lower generalizability of the findings from the here proposed enrichment strategy is justified by the fact that this group of AD patients is responsible for the majority of AD attributable burden (Rehm et al., 2018). Furthermore, the limitation of reduced generalizability can be handled with a restriction of the indication to the high-severity population for medicinal products which have demonstrated efficacy and a positive benefit-risk in the enriched population. In this respect and while the clinical development included both populations, nalmefene efficacy in the treatment of AD was established in the high-severity population only and the compound was consecutively approved by the EMA in this restricted population which excludes L/M DRL patients and early abstainers/reducers (European Medicines Agency, 2012). We, therefore, are in favor of the use of population enrichment strategies to improve assay sensitivity in trials with alcohol use disorder patients. In conclusion, the present work supports the use of population enrichment approaches to improve assay sensitivity in clinical trials with AD patients. The goal of such an approach is to enroll only patients with the highest probability to benefit from pharmacological treatments, thus improving our ability to develop novel precision medicines.

CONFLICT OF INTERESTS

Giovanni Addolorato served as a consultant for Ortho-McNeil Janssen Scientific Affairs, LLC, and D&A Pharma, and was paid for his consulting services. He has received lecture fees from D&A Pharma. Henri-Jean Aubin reports being member of advisory boards or DSMB for Bioprojet, and Ethypharm, and has received sponsorship to attend scientific meetings, speaker honoraria or consultancy fees from Bioprojet, D&A Pharma, Ethypharm, Kinnov Pharmaceuticals and Lundbeck. He is also member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative (ACTIVE), which was supported in the last three years by Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Indivior, Lundbeck, Mitsubishi, and Otsuka. Rolland Benjamin received fees from Ethypharm and Lundbeck. David Nutt reports personal fees from D&A Pharma and Lundbeck and is a director of Alcarelle. Wim van den Brink reported personal fees from D&A Pharma, Kinnov Therapeutics, Bioproject, Lundbeck, Novartis, Indivior, Angelini, Mundipharma, Takeda, and Opiant Inc. Maurice Dematteis has provided expert advice to Bouchara-Recordati Laboratories, Camurus, Indivior, Lundbeck and D&APharma, and received fees for lectures from Bouchara-Recordati Laboratories, Lundbeck, Camurus and Indivior. Antony Gual reports grants from Novartis and D&A Pharma. Lorenzo Leggio is a U.S. federal employee and is supported by the NIDA and NIAAA intramural research programs. He has also received royalties from Routledge Press (textbook) and honoraria from the UK Medical Council on Alcoholism (Editor-in-Chief for Alcohol and Alcoholism). Jürgen Rehm reported personal fees from D&A Pharma and Lundbeck. Rainer Spanagel reported grants from Horizon 2020 program, Era-NET NEURON, BMBF, Deutsche Forschungsgemeinschaft (DFG), and personal fees from EMCCDA and D&A Pharma during the conduct of the study. Bruno Scherrer reported fees from D&A pharma, DNDI, HRA Pharma and other pharmaceutical organizations.

JG is employed by D&A Pharma which was one sponsor of this study. RP and QR were employed by D&A Pharma. The other funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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CHAPTER 5

Sodium oxybate for alcohol dependence:a network meta-regression analysis considering population severity at baseline and treatment duration

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ABSTRACT

Aims: The estimated effect of sodium oxybate (SMO) in the treatment of alcohol dependence is heterogeneous. Population severity and treatment duration have been identified as potential effect modifiers. Population severity distinguishes heavy drinking patients with <14 days of abstinence before treatment initiation (high-severity population) from other patients (mild-severity population). Treatment duration reflects the planned treatment duration. This study aimed to systematically investigate the effect of these potential effect moderators on SMO efficacy in alcohol dependent patients.

Methods: Network meta-regression allows for testing potential effect modifiers. It was selected to investigate the effect of the above factors on SMO efficacy defined as continuous abstinence (abstinence rate) and the percentage of days abstinent (PDA). Randomized controlled trials for alcohol dependence with at least one SMO group conducted in high-severity and mild-severity populations were assigned to a high-severity and mild-severity group of studies, respectively.

Results: Eight studies (1,082 patients) were retained: four in the high-severity group and four in the mild-severity group. The high-severity group was associated with larger SMO effect sizes than the mild-severity group: abstinence rate RR 3.16, p=0.004; PDA +26.9%, p<0.001. For PDA, longer treatment duration was associated with larger SMO effect size: +11.3% per extra month, p<0.001. In the high-severity group, SMO showed benefit: abstinence rate RR 2.91, p=0.03; PDA +16.9%, p<0.001. In the mild-severity group, SMO showed benefit only in PDA for longer treatment duration: +23.9%, p<0.001.

Conclusions: In the retained studies with alcohol-dependent patients, high-severity population and longer treatment duration were associated with larger SMO effect sizes.

INTRODUCTION

Alcohol dependence (AD) is responsible for about two-thirds of the overall alcohol-attributable mortality (Rehm and Shield, 2012). There is strong evidence that alcohol-related harm is mainly determined by the amount of alcohol consumed and the drinking pattern (Rehm et al., 2018, 2012, 2010).

One of the treatment goals for AD is abstinence (European Medicines Agency, 2010). Currently, disulfiram, acamprosate and naltrexone are registered for the maintenance of abstinence in AD patients. Although effective on the group level, effects sizes are heterogeneous and limited, and many AD patients fail to respond to these medications (European Medicines Agency, 2010; van den Brink et al., 2018). Therefore, additional pharmacological treatments are needed.

Sodium oxybate (SMO) as an oral solution has been approved in Italy and Austria for the treatment of alcohol withdrawal syndrome and for maintenance of abstinence since 1991 and 1999, respectively (van den Brink et al., 2018). SMO is the sodium salt of γ-hydroxybutyric acid (GHB), a short-chain fatty acid that is naturally synthesized in the mammalian brain. SMO is a low affinity agonist at GABAB receptors and also binds with high affinity to GHB-specific binding sites (Keating, 2014; Leurs et al., 2021; van den Brink et al., 2018). One proposed mechanism of SMO in the treatment of AD is its ability to mimic some effects of alcohol in the brain (Kamal et al., 2016; Keating, 2014). SMO showed evidence of efficacy compared with placebo or naltrexone in AD patients in a series of randomized controlled trials (RCTs), including a Phase III trial, and in various (network) meta-analyses (Caputo et al., 2007, 2003; Cheng et al., 2020; Gallimberti et al., 1992; Guiraud et al., 2022; Leone et al., 2010; van den Brink et al., 2018). However, heterogeneity of the SMO treatment effect was identified within and across studies (Guiraud et al., 2022, 2021; van den Brink et al., 2018). In a recent network meta-analysis including 64 trials (43 interventions), evidence of inconsistency of SMO treatment effect between direct and indirect comparisons was identified (Cheng et al., 2020) suggesting an unbalanced presence of effect modifier(s) across studies in the network (Dias et al., 2011). No evidence was found of heterogeneity being explained by meta-regression on predefined study level characteristics (Cheng et al., 2020). In another meta-regression analysis, including 51 RCTs for AD, treatment effect of approved medications for AD was significantly negatively correlated with the magnitude of the placebo response. No effect modifiers were identified among the factors tested (Litten et al., 2013). Interestingly, these meta-regressions did not test the effect of population severity and (planned) treatment duration, two factors identified as effect modifiers of several approved medications for AD and/or predictors of placebo response.

Population severity distinguishes AD patients with heavy alcohol consumption (>40g/day for women and >60g/day for men) at baseline and with a short abstinence duration (<14 consecutive days) before treatment initiation from other AD patients. With respect to their level of response to placebo treatment, these patients have been defined in the literature as the high-severity population and the complement population as the mild-severity population (Scherrer et al., 2021; van den Brink et al., 2018). Recent subgroup analyses in studies for the treatment of AD showed that the placebo response in double-blind RCTs is lower and treatment effect size is higher in the high-severity population than in the mild-severity population (Mann et al., 2016; Pierce et al., 2018; Scherrer et al., 2021; van den Brink et al., 2018, 2014, 2013). Furthermore, longer planned treatment durations were associated with lower placebo response within and across RCTs conducted in populations with a certain severity level (Scherrer et al., 2021).

Therefore, the aim of this study was to simultaneously investigate the potential moderating effect of population severity and treatment duration on SMO efficacy in RCTs directed at the maintenance of abstinence in AD patients. A method to test these interactions across studies is network meta-regression (NMRA) (Higgins et al., 2022) and thus, this analysis was selected to systematically investigate SMO efficacy heterogeneity in the treatment of AD. In addition, separate analyses were performed to assess the credibility and plausibility of our findings.

METHODS

The protocol for this review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022347817).

Eligibility criteria

We included all published RCTs conducted in AD patients to maintain abstinence in an outpatient setting and which included at least one group treated with SMO. Only full text articles in English were selected.

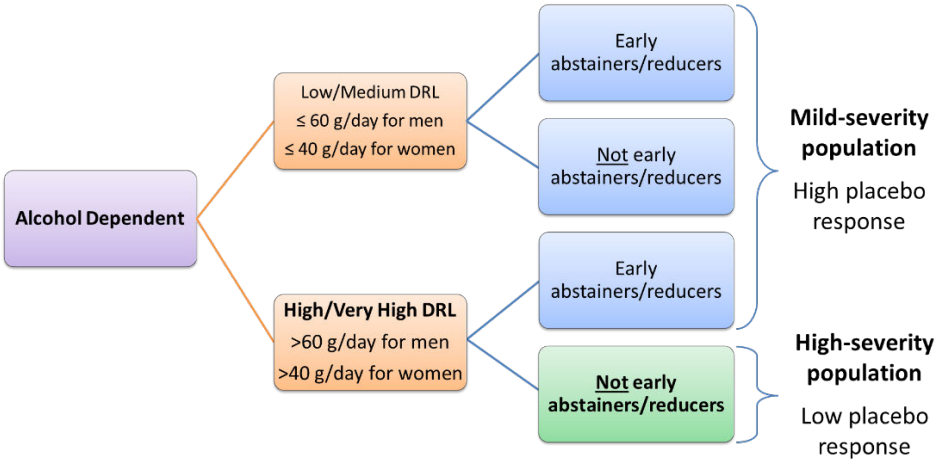
Population

Selected studies included AD patients according to DSM (IV or earlier), ICD (10 or earlier) or equivalent criteria. Patients needed to be abstinent before starting the study medication.

Determination of population severity and treatment duration

For those articles not reporting efficacy separately for severity subgroups, studies were assigned to one of the severity groups with the Scherrer et al. (2021) method: studies reporting a long abstinence duration before treatment and/or non-heavy alcohol consumption at baseline at study level were assigned to the group of mild-severity studies (Figure 1). Studies reporting a short abstinence duration before treatment and heavy alcohol consumption at baseline at study level were assigned to the group of high-severity studies (Figure 1). For studies reporting on efficacy separately for each severity subgroup, data of each subgroup (mild-severity and high-severity) were treated as a standalone study allocated to the group of mild-severity or the group of high-severity studies, respectively.

Figure 1. Definitions of alcohol dependent subpopulations according to van den Brink et al. (2018)



DRL: drinking risk level; early abstainers: patients with more than 14 consecutive days of abstinence before treatment initiation; early reducers: patients who reduce their alcohol consumption to a low or medium DRL prior to treatment initiation;

Treatment duration was a continuous variable expressed in months and reflecting the planned treatment duration for each retained RCT. See supplementary material for additional information.

Interventions/comparators

All studies with SMO as one of the pharmacological interventions for maintaining abstinence in AD patients in an outpatient setting were included in the analysis. In a network meta-analysis each treatment is compared directly and/or indirectly with all other treatments, therefore any treatment can be the comparator. In the current report placebo was used as main comparator (Figure 3).

Outcome

The selected primary outcome was the abstinence rate which is the primary endpoint recommended by regulatory agencies for the demonstration of efficacy in the maintenance of abstinence (European Medicines Agency, 2010; US Food and Drug Administration, 2015). Our definition of abstinence was continuous abstinence (no relapse to any alcohol use) throughout the treatment period.

In accordance with the European Medicines Agency (EMA) guideline, the percentage of days abstinent (PDA) was selected as a secondary measure (European Medicines Agency, 2010). If cumulative abstinence duration was reported and PDA was not reported and since both endpoints are closely related, the cumulative abstinence duration was transformed into PDA by dividing the reported cumulative abstinence duration in each treatment group by the planned treatment duration. Other outcomes were reported in no more than two studies and were, thus, not included in the analyses.

Search strategy

We performed a systematic search considering articles assessed for eligibility (after exclusion of duplicates) in previous systematic reviews and meta-analyses with similar research questions related to similar populations (AD) and study designs (RCTs) as our NMRA (Figure 2 and full list in supplementary material). However, since these searches only covered articles published up to March/October 2020, we also conducted a systematic screening of original articles published from March 2020 to July 2022 in MEDLINE based on PRISMA guidelines (see search strategy in supplementary material).

Study selection

Articles identified through this search strategy were screened by three reviewers and information related to the inclusion/exclusion criteria are presented in a bespoke Excel spreadsheet. Any disagreement between reviewers or uncertainty related to the study selection was discussed and resolved.

Data extraction

Data were extracted from the publication in duplicate in a pre-piloted Excel spreadsheet and were reviewed by a third reviewer. When multiple articles from one study existed, all reports were considered, data were retrieved from these different sources and the related articles were referenced in the Excel spreadsheet.

Dealing with missing data

We used results from the intention-to-treat population. Since relapse was the main documented reason for dropout in previous trials (Guiraud et al., 2022), dropouts were treated as treatment failures for abstinence rate (patient not continuously abstinent) in all retained studies. For PDA, we used the efficacy results and thus the imputation method for missing data reported in the article.

Assessment of risk of bias

The revised Cochrane risk-of-bias tool for randomized trials (RoB2) (Sterne et al., 2019) was used to assess the risk of bias in five domains: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Three reviewers conducted the assessment of the risk of bias. Any disagreement between reviewers or uncertainty was discussed and resolved. Information supporting the risk of bias assessment was presented in a bespoke Excel spreadsheet (see supplementary material).

Data synthesis

SMO efficacy was investigated using a NMRA with population severity and treatment duration as covariates and was then explored in each population severity group separately using a network meta-analysis. Network meta-analysis is a technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies. NMRA is a technique to investigate whether certain study characteristics are associated with the intervention effects in the network meta-analysis (Higgins et al., 2022).

To address the risk of overfitting, a sensitivity analysis using a NMRA with only population severity as a covariate was conducted for the primary endpoint on the overall sample of retained studies. A second sensitivity analysis using NMRA was performed with only double-blind RCTs.

Results for all comparisons were synthetized using risk ratio (RR) for abstinence rate and mean difference for PDA, including the 95% confidence interval. For evaluations of consistency in the network, we used the design-by-treatment interaction model (Higgins et al., 2012). Analyses assumed random effects for intervention effects within a frequentist framework.

The statistical software that we used was STATA® SE 14.2. NETWORK META was used for performing NMRA and network meta-analysis models.

Credibility and plausibility of findings

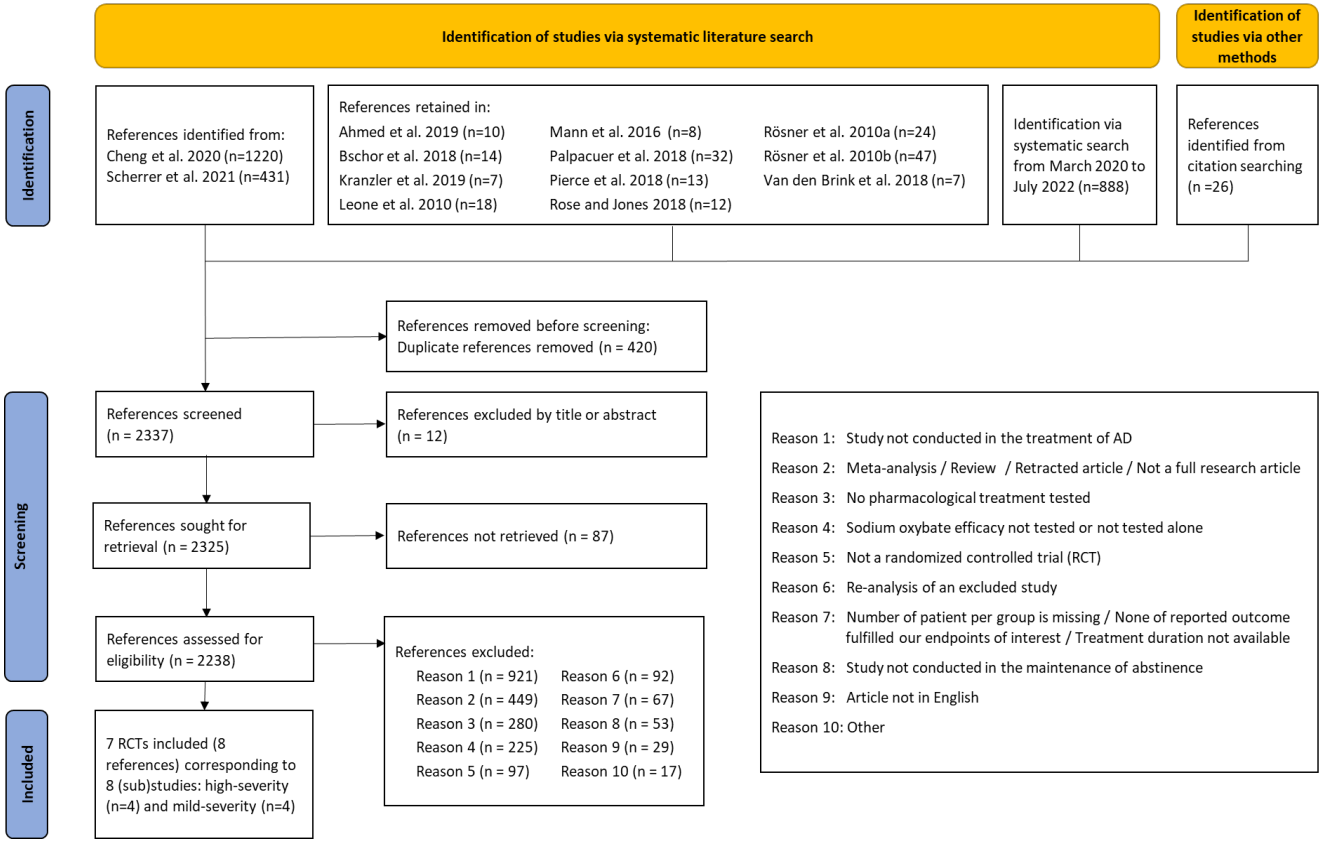
The following criteria defined by the EMA and the Cochrane were used to assess the reliability of the subgroup findings: i) a statistically persuasive and clinically relevant treatment effect has to be demonstrated in the whole population, ii) existence of external evidence defining the subgroup of interest, iii) existence of a pharmacological rationale of the difference of treatment effect between subgroups, iv) the magnitude of the difference of treatment effect between subgroups is statistically significant and practically important, v) differences of treatment effect between subgroups are observed within and between studies and existence indirect evidence in support of the findings, and vi) the subgroup analysis was pre-specified (European Medicines Agency, 2019; Higgins et al., 2022). See supplementary material for additional information.

RESULTS

Study selection

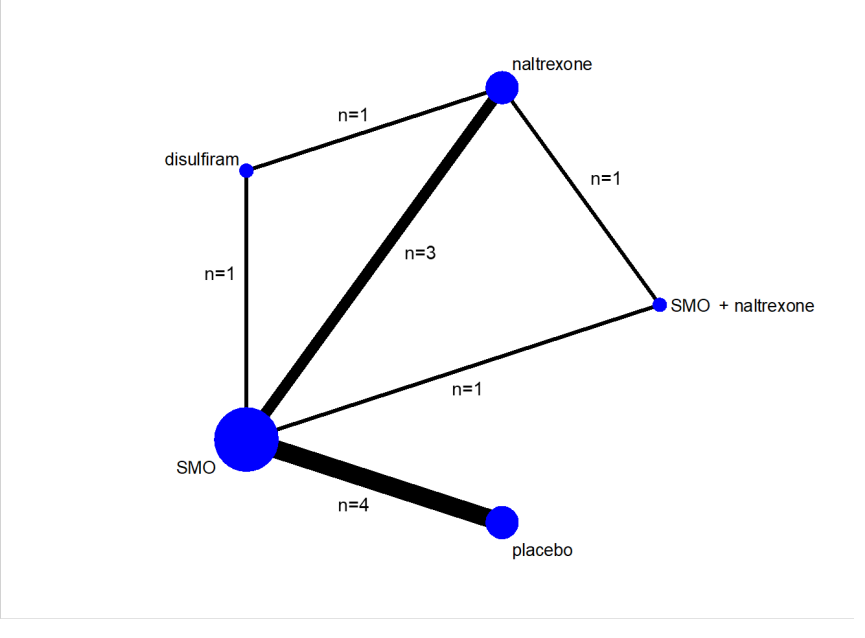
In total 2337 references were screened and 2329 were excluded. The main reasons for exclusion were the following: study not about the treatment of AD (n=921), review, meta-analysis, retracted article, not a full-length original research paper (e.g. conference paper, poster) (n=449), no pharmacological treatment tested (n=280), and SMO efficacy not tested (n=225) (Figure 2 – see list in supplement).

Figure 2. Flow diagram of study selection



Seven RCTs (reported in eight references) totalling 1,082 treated patients fulfilled the selection criteria and were included: four double-blind, placebo-controlled trials testing SMO efficacy and safety (Di Bello et al., 1995; Gallimberti et al., 1992; Guiraud et al., 2022, 2021; van den Brink et al., 2018), one open-label RCT comparing SMO to naltrexone (Caputo et al., 2003), one open-label study comparing SMO to naltrexone and the combination of SMO and naltrexone (Caputo et al., 2007), and one open-label study comparing SMO to naltrexone and disulfiram (Nava et al., 2006) (Figure 3). All retained studies reported the abstinence rate in each treatment group whereas three (double-blind placebo controlled) RCTs reported PDA or the cumulative abstinence duration (Gallimberti et al., 1992; Guiraud et al., 2022, 2021). The retained RCTs recruited patients from sites in 9 European countries. See supplementary material Table S.2 for additional information on included studies.

Figure 3. Network plot of efficacy studies in abstinence rate



SMO: sodium oxybate. Nodes represent the interventions in the network and lines show the available direct comparisons between pairs of interventions, e.g., SMO vs. placebo. The size of the nodes corresponds to the number of participants assigned to each treatment. The thickness of the line and the reported number both indicate the number of trials evaluating the specific comparison.

Risk of bias assessment

Risk of bias assessment showed a low risk or only some concerns for all domains except for the risk of bias due to missing outcome data and for the risk of bias in measurement of the outcome. The dropout rates and the lack of sensitivity analyses for missing data imputation may have affected the treatment effects for four studies, although we considered dropout as relapse/failure for abstinence rate analysis. The high-risk bias in measurement of the outcome for five studies was mainly due to the treatment allocation not being blind in four studies (supplementary material Table S.3).

Study allocation to population severity subgroups

One RCT recruited both mild-severity and high-severity patients and the related article reported efficacy data per severity subgroups (Guiraud et al., 2021). For this RCT, each population severity subgroup was considered as a standalone study in the NMRA and was assigned to the group of mild-severity and high-severity studies, respectively. In addition, three RCTs were allocated to the mild-severity group of studies whereas three RCTs were allocated to the high-severity group of studies (see Table S.2). Consequently, the mild-severity group in the NMRA consisted of 4 (sub)studies totalling 756 patients and 4 (sub)studies totalling 326 patients were allocated to the high-severity group (Table 1).

Main characteristics of retained studies

Mean age at baseline, percentage of men, and mean alcohol consumption at baseline were similar in the two population severity subgroups. However, mean abstinence duration before treatment initiation in the high-severity and in the mild-severity group of studies were very different: 4.7 and 17.4 days, respectively (Table 1). The assignment of studies to the mild-severity group was driven by a long abstinence duration before treatment initiation for three studies and by a non-heavy alcohol consumption at baseline for one study (Table S.2). Other baseline characteristics scores were available in less than two studies or were expressed differently (e.g., categories vs mean score) and are not reported here.

Table 1. Descriptive statistics and main characteristics in retained studies

Characteristics	Statistical parameters	Overall	Mild-severity population	High-severity population
Retained studies	N studies	8	4	4
Sample size	N patients total	1 082	756	326
	Mean (SD)	135 (125)	189 (162)	82 (52)
	Min; Max	17; 339	17; 339	35; 154
Treatment duration (months)	Mean* (SD)	4.9 (3.2)	6.8 (3.8)	3.0 (0.0)
	Min; Max	3.0; 12.0	3.0; 12.0	3.0; 3.0
Mean age of patients (years)	Mean* (SD)	45.2 (4.1)	44.7 (2.9)	45.6 (5.5)
	Min; Max	37.5; 48.8	40.7; 47.3	37.5; 48.8
% males	Mean* (SD)	75.7 (7.4)	80.3 (3.4)	71.1 (7.7)
	Min; Max	63.0; 84.8	76.5; 84.8	63.0; 78.2
Mean alcohol consumption at baseline (g/day)**	Mean* (SD)	103.0 (36.4)	95.9 (41.3)	113.6 (38.8)
	Min; Max	48.2; 141.1	48.2; 121.2	86.1; 141.1
Mean abstinence duration prior to treatment (days)**	Mean* (SD)	11.0 (9.7)	17.4 (10.3)	4.7 (2.6)
	Min; Max	1.0; 30.0	5.5; 30.0	1.0; 7.0

*Unweighted estimate; **the threshold values from inclusion/exclusion criteria regarding alcohol consumption at baseline and/or abstinence duration prior to treatment initiation were used for descriptive statistics computation for studies not reporting mean values (see supplementary material);
In the overall population, the mild- and high-severity subgroups from the RCT conducted by Guiraud et al. (2021) were considered as standalone studies for the computation of descriptive statistics.

Primary analysis

In the main analysis, simultaneously including population severity and treatment duration as covariates, the SMO treatment effect in abstinence rate (compared to placebo) was significantly dependent on population severity (p=0.004) and it was increased by a RR (95%CI) of 3.16 (1.45; 6.85) in the high severity group of studies compared to SMO treatment effect in the mild-severity group of studies (Table 2). In this analysis, treatment duration was not a significant effect modifier of SMO in abstinence rate (p=0.139; Table 2). The sensitivity analysis using only double-blinded RCTs provided very similar results as the main analysis, both in terms of point estimates and statistical significance. The NMRA using only population severity as covariate also showed a significant effect of population severity on SMO treatment effect in abstinence rate with a point estimate very similar to the one in the main analysis.

Table 2. Effect of population severity and treatment duration on sodium oxybate versus placebo treatment effect

Covariates	Estimate	95% CI	p value
Main analysis: abstinence rate, 8 studies, 18 arms, 1082 participants			
Population Severity	RR 3.16	1.45 to 6.85	p=0.004
Treatment Duration	RR 1.14	0.96 to 1.35	p=0.139
Secondary analysis: PDA, 4 studies, 8 arms, 878 participants			
Population Severity	MD 26.9%	17.5 to 36.2	p<0.001
Treatment Duration	MD 11.3%	6.0 to 16.5	p<0.001

RR: risk ratio; MD: mean difference; CI: confidence interval; PDA: percentage of days abstinent

Secondary analysis

In the secondary analysis, simultaneously including population severity and treatment duration as covariates, the SMO treatment effect in PDA (compared to placebo) was also dependent on population severity (p<0.001) and the SMO treatment effect was increased by a mean difference of +26.9% in the high severity group compared to SMO treatment effect in the mild-severity group (Table 2). In contrast to the abstinence rate analysis, SMO efficacy in PDA was also significantly dependent on treatment duration: SMO treatment effect in PDA in a given severity group was increased by +11.3% per extra month of treatment duration (p<0.001) (Table 2).

Network meta-analysis separately for each population severity subgroup

Given these results, the SMO treatment effect (compared to placebo) was further investigated using a network meta-analysis conducted separately in each severity group for abstinence rate and in each severity group and according to treatment duration for PDA. In the high severity population and compared to placebo, SMO showed a clinically relevant effect in abstinence rate (RR 2.91; 95%CI 1.11 to 7.65) and in PDA after a 3-month treatment duration (mean difference +16.9%; 95%CI 10.9 to 23.0). In the high severity population, the combination SMO and naltrexone was also superior to placebo in abstinence rate (RR 5.94; 95%CI 1.42 to 24.96).

However, in the mild-severity population, the magnitude of the effect was numerically in favor of placebo for naltrexone and disulfiram and placebo was significantly superior to SMO in PDA at 3 months (Table 3). The exception was a significant benefit for SMO compared to placebo in PDA in the mild severity population after a 6-month treatment duration (mean difference +23.9%; 95%CI 15.9 to 32.0) (Table 3).

No evidence of inconsistency based on a random effects design-by-treatment interaction model was found in the network meta-analysis conducted in the high-severity group of studies (χ^2=1.31, p=0.25) or in the mild-severity group of studies (χ^2=0.14, p=0.71).

Credibility and plausibility of findings

Data support fulfilment of the EMA and Cochrane criteria for credibility and the plausibility of the findings: i) SMO showed efficacy in the whole study population ; ii) external evidence for the definition of the selected subgroups exists; iii) a pharmacological rationale of the difference of treatment effect between subgroups exists; iv) the difference between subgroups was clinically important and statistically significant and treatment effect in the high-severity was larger than in the mild-severity group, v) effects of population severity and treatment duration on SMO efficacy have been observed within and across trials and are supported by external evidence from trials on other AD medications; vi) the protocol for this review was registered in PROSPERO. See supplementary material for the empirical justification of these statements and the supporting literature references.

Table 3: Treatment effect of active compounds vs. placebo in each population severity group for abstinence rate and per population severity and treatment duration for PDA

Analysis	Treatment	No of arms*	No of participants*	Estimate (95% CI)	p value
Primary outcome: abstinence rate					
High-severity group of studies	SMO+NTX	1	18	RR 5.94 (1.42 to 24.96)	p=0.015
	SMO	4	192	RR 2.91 (1.11 to 7.65)	p=0.030
	NTX	2	34	RR 1.22 (0.35 to 4.28)	p=0.751
Mild-severity group of studies	SMO	4	473	RR 1.06 (0.77 to 1.47)	p=0.706
	NTX	1	27	RR 0.80 (0.42 to 1.51)	p=0.484
	DSF	1	31	RR 0.64 (0.33 to 1.25)	p=0.192
Secondary outcome: PDA					
High-severity - 3 months Tx	SMO	2	149	MD +16.9% (10.9 to 23.0)	p<0.001
Mild-severity – 3 months Tx	SMO	1	282	MD -9.9% (-17.7 to -2.2)	p=0.012
Mild-severity – 6 months Tx	SMO	1	154	MD +23.9% (15.9 to 32.0)	p<0.001

SMO: sodium oxybate; DSF: disulfiram; NTX: naltrexone; Tx: treatment duration; RR: risk ratio; MD: mean difference; CI: confidence interval; PDA: percentage of days abstinent;
* mild severity group included three placebo arms (225 participants) and high-severity group included two placebo arms (82 participants);

DISCUSSION

SMO has shown evidence of efficacy in the treatment of AD in a series of RCTs and meta-analyses and treatment with SMO is safe and well-tolerated (Addolorato et al., 2020; van den Brink et al., 2018). However, substantial heterogeneity of SMO treatment effects has been identified within and across studies (Guiraud et al., 2022, 2021; van den Brink et al., 2018). Heterogeneity in the efficacy of pharmacotherapies is common in the treatment of AD (Litten et al., 2013; Rösner et al., 2010; Scherrer et al., 2021; van den Brink et al., 2018). It is, therefore, important to determine the moderators of the treatment effect as well as the target population in which these medications are (most) effective.

Here we studied population severity and treatment duration as two potential effect modifiers of SMO using NMRA. Population severity is a categorical variable with two categories that have been defined in literature as a potential effect modifier. It distinguishes heavy drinkers without "spontaneous improvement" before treatment initiation (high-severity) from other patients (mild-severity) (Scherrer et al., 2021; van den Brink et al., 2018). Treatment duration is a continuous variable reflecting the planned treatment duration in the retained studies.

In our NMRA of 8 studies with 1,082 treated AD patients, the effect of SMO compared to placebo was dependent on population severity and was increased in the high-severity group of studies compared to the group of mild-severity: RR 3.16 ($p=0.004$) for abstinence rate and mean difference +26.9% ($p<0.001$) for PDA. The relationship between SMO treatment effect and treatment duration was not significant ($p=0.139$) for the abstinence rate analysis, but it was significant for the PDA analysis with an increase of 11.3% per extra month of treatment duration ($p<0.001$). It should be recognized, however, that meta-regressions have low power to detect relationships (especially with dichotomous outcomes) and that at least 10 studies are generally required to detect a modifier effect (Higgins et al., 2022).

In the high-severity group of studies, SMO showed a clinically meaningful benefit vs. placebo both in abstinence rate (RR 2.91) and in PDA (mean difference + 16.9%). In contrast, no clinically relevant benefit in abstinence rate vs. placebo was shown in the mild-severity population. In this population, placebo was significantly superior to SMO in PDA at 3 months. This result is explained by data from the Guiraud et al. (2021) RCT where the placebo response in PDA at 3 months in the mild-severity subgroup was very high (mean 87.2%) and higher than in SMO group (mean 77.3%) (see supplementary material). The exception was a positive and clinically relevant effect of SMO in PDA for a treatment duration of 6 months in the mild-severity group, illustrating the

significant effect of treatment duration on SMO efficacy in this endpoint. The placebo response in PDA was much lower for a 6-month than for a 3-month treatment duration in the mild-severity group (mean 37.9% vs. 87.2% - see supplementary material). At treatment group level, PDA measures the differences in abstinence rate as well as the differences in abstinence duration in relapsing patients. The significant beneficial effect of SMO in PDA in the mild severity population at 6 months can probably be explained by the combination of a longer abstinence duration in relapsing patients and a numerically higher abstinence rate in the SMO compared to the placebo group (Guiraud et al., 2022). Therefore, and in our network meta-analysis, SMO efficacy in PDA in the high-severity group of studies was mainly explained by a beneficial effect of SMO in abstinence rate whereas, in the mild-severity group of studies, the beneficial effect of SMO in PDA at 6 months was mainly driven by a longer abstinence duration in relapsing patients and a numerically higher abstinence rate.

Fortunately, and in contrast to a recent network meta-analysis (Cheng et al., 2020) that did not adjust treatment effects for population severity and treatment duration, no evidence of inconsistency between direct and indirect estimates of SMO treatment effects was found in the present network meta-analyses, suggesting that population severity and treatment duration are important sources of inconsistency. The lack of evidence of inconsistency may also be due to the small number of studies retained.

The present NMRA investigates differences between studies and individuals were not randomized to go in one trial or another. Hence, this analysis is observational with a risk of bias by confounding, chance findings, and aggregation bias, especially when the sample of studies retained is relatively small compared to the number of covariates/moderators tested (Higgins et al., 2022). To address these risks, it is important to assess the reliability of the findings. The EMA and the Cochrane provided criteria to be fulfilled to reduce the risk of false causal relationship in meta-regression and to assess the credibility and the plausibility of exploratory subgroup findings (European Medicines Agency, 2019; Higgins et al., 2022). Our data support the fulfilment of these criteria and, thus, a probable causal relationship between the tested covariates (population severity and treatment duration) and SMO treatment effect seems to exist.

The sensitivity analysis using only double-blind studies provided very similar results as the main analysis and the assignation of these studies to the population severity groups was only based on inclusion/exclusion criteria (see Table.S.2). These data support a low risk of aggregation bias and indicate that results of the main analysis were not markedly affected by the potential bias due to the lack of blinding in some studies.

Drop-out rates in the retained studies were relatively high and were consistent with those commonly observed in AD trials and those in 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 treatment failures in the analysis of abstinence rate and relapse was the main documented reason for dropout in previous trials (Guiraud et al., 2022).

The combination of SMO and naltrexone showed promising results in abstinence rate in the high-severity group whereas naltrexone and disulfiram did not show any significant benefit in both severity populations. These results have limitations and should be interpreted with caution since they were based on only one direct comparison with a small sample size for most of these interventions.

In conclusion, the present work provides data to explain heterogeneity of SMO efficacy in the treatment of AD. Results support the efficacy of SMO independent of treatment duration in high-severity populations and of long-term SMO treatments in mild-severity populations. Our results may help healthcare providers in the use of SMO for the treatment of AD. Other subgroupings, e.g., according to genetic, neurobiological, and other clinical features, might also be important effect modifiers of SMO (Lesch et al., 2020). They need to be further investigated to improve precision medicine for AD patients.

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Julien Guiraud is employed by Vergio, Clichy, France. Sylvie Lecoustey and Sylvie Bachelot are employed by D&A Pharma, Paris, France.

Wim van den Brink reports personal fees from D&A Pharma, Kinnov Therapeutics, Bioproject, Lundbeck, Novartis, Indivior, Angelini, Mundipharma, Takeda, Opiant Inc, Recordati, Camurus, Novo Nordisk, and Clearmind Medicine.

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Otto Lesch served as a paid consultant for D&A Pharma. He was investigator in the SMO032 study (Guiraud et al., 2021) and in the GATE 2 study (Guiraud et al., 2022).

Icro Maremmani served as board member for Angelini, Camurus, CT Sanremo, D&A Pharma, Gilead, Indivior, Lundbeck, Molteni, MSD, Mundipharma.

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Andrea de Bejczy is founder and co-owner of Sobrera Pharma AB. She was investigator in the SMO032 study (Guiraud et al., 2021).

Philippe Batel reported fees from Lundbeck, D&A pharma, Kinnov therapeutics. He was investigator in the SMO032 study (Guiraud et al., 2021).

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CHAPTER 6

Alcohol dependence and very high risk level of alcohol consumption: a life-threatening and debilitating disease

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ABSTRACT

Women and men with alcohol dependence and very high risk drinking level (VHRDL; defined as drinking >60 or 100 g of ethanol per day, respectively) experience severe health consequences; however, data on the number of these individuals and their health risks are limited. This study estimated (1) the prevalence of VHRDL in 13 European Union (EU) countries among people 15–65 years of age, (2) the risk of disease and injury occurrence associated with VHRDL, (3) the proportion of deaths in nine EU countries attributable to VHRDL and (4) the life expectancy of people in France with VHRDL. Prevalence estimates of VHRDL were based on data obtained from clinical trials and the Global Information System on Alcohol and Health. The risk of disease and injury occurrence was estimated using microsimulations. Population-attributable fractions (PAFs) were estimated using a Levin-based methodology. The estimated prevalence of VHRDL in the 13 EU countries examined was 0.74–0.85 percent, with a disease and injury occurrence risk of 13.5 per 100 people with VHRDL per year. For the nine EU countries examined, VHRDL caused 53.6 percent of all liver cirrhosis, 43.8 percent of all pancreatitis and 41.1 percent of oral cavity and pharyngeal cancers (all other PAFs were below 30 percent). Applying these PAFs to French mortality data resulted in a life expectancy of 47–61 years for people with VHRDL—21–35 years less than the general population. These results indicate that the health burdens of VHRDL are potentially large, and interventions targeting VHRDL should be considered when formulating public health policies.

INTRODUCTION

Two billion people globally consume alcohol, leading in 2016 to 2.8 million deaths (5.2% of all deaths) and 99.2 million Disability Adjusted Life Years (DALYs) lost (4.2% of all DALYs) (GBD 2016 Risk Factors Collaborators, 2017). Of all the diseases, conditions, and injuries attributable to alcohol use, alcohol use disorders (AUDs) create the largest health burden globally (World Health Organization 2014). AUDs are diagnostically characterized by a strong desire or compulsion to drink alcohol despite knowledge or evidence of its harmful consequences and by difficulty in controlling drinking in terms of onset, termination or levelling of its use, physiological withdrawal symptoms, and development of tolerance (World Health Organization, 1993). However, people with AUDs constitute a highly heterogeneous population with different levels of severity, categorized as "harmful alcohol use" and "alcohol dependence" in the ICD-10, as "alcohol abuse" and "alcohol dependence" in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, and as "mild," "moderate," and "severe" AUD in the DSM-5. Moderate dependence is characterized by a raised level of tolerance (needing to drink more to reach the same level of intoxication), some symptoms of withdrawal, and impaired control over drinking. Severely dependent patients additionally exhibit relief drinking, morning drinking, stereotypical drinking, as well as blackouts (European Medicines Agency, 2010). People with alcohol dependence (AD) sustain high alcohol consumption, and thus are at high-risk for acute and chronic health consequences. The past year prevalence of AD is estimated at 5-6% in men and 1-2% in women in the European Union (EU) (European Medicines Agency, 2010; Rehm et al., 2015), resulting in 11 million people 18 to 64 years of age with AD in 2010. Consequently, a substantial part of the overall alcohol-attributable mortality burden in the EU (62% - 71% dependent on the assumptions) is due to alcohol-dependent subjects (Rehm et al., 2013, 2012).

There is strong evidence that with very few exceptions alcohol-related harms are determined by the volume of alcohol consumed, and the risk of disease occurrence increases in an exponential dose response manner and accumulates over time (Laramée et al., 2014; Jürgen Rehm et al., 2017; Shield et al., 2013). Volume of alcohol consumption has been categorized into different risk levels by the World Health Organization (WHO) and the European Medicines Agency (EMA) (Table 1).

Table 1. World Health Organization criteria for risk of consumption on a single drinking day in relation to acute problems

Drinking level category	Average daily consumption of ethanol (grams per day)	
	Male	Female
Low risk	>0 to ≤40	>0 to ≤20
Moderate risk	>40 to ≤60	>20 to ≤40
High risk	>60 to ≤100	>40 to ≤60
Very high risk	>100	>60

Source: (European Medicines Agency, 2010c; World Health Organization, 2000)

People with AD and with a daily alcohol consumption at very high risk drinking levels (VHRDL) can be considered as the most severely affected population of alcohol users as (i) the volume of alcohol consumed and the pattern of drinking have the greatest toxicity on the organs and tissues, (ii) subjects are chronically intoxicated, leading to daily or almost daily impairment of psychomotor coordination, cognition, perception, and affect and/or behaviour, and (iii) the dependence on the substance sustains a very high level of alcohol consumed despite knowledge or evidence of its harmful consequences.

The size of the alcohol-dependent population with VHRDL has never been studied in detail. In a recent large clinical trial with 60 sites in 10 European countries, allowing for the recruitment of alcohol-dependent patients regardless of their drinking risk levels, the proportion of alcohol-dependent patients with a VHDRL represented 21.7% of the alcohol-dependent population (van den Brink et al., 2014). Data from the COMBINE study – a clinical trial that evaluated combinations of medications and behavioural interventions in the treatment of AD – showed that the majority of individuals (59%) were in the VHRDL category (Witkiewitz et al., 2017).

Given the lack of information on VHRDL in the general population, the present study aimed to estimate (i) the prevalence of and the number of people with VHRDL in 13 EU countries (Austria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, the Netherlands, Spain, Sweden, and the United Kingdom (UK)), (ii) the risk of disease and injury occurrence among people with VHRDL, (iii) the proportion of the alcohol-attributable disease and injury burden caused by the co-occurrence of AD and VHRDL in 9 EU countries (Austria, Denmark, Finland, France, Ireland, the Netherlands, Spain, Sweden, and the United Kingdom), and (iv) the life expectancy of people with both AD and VHRDL, using France as an example.

METHODS

Estimation of the prevalence of VHRDL using data from population surveys and clinical trials

Two approaches were used to assess the prevalence and the number of alcohol-dependent people with a VHRDL. First, the prevalence of AD patients with VHRDL was estimated by combining general population data on the prevalence of AD obtained from the Global Information System on Alcohol and Health (GISAH) (World Health Organization, 2018) with data from a clinical trial of people with AD in EU countries (van den Brink et al., 2014). This approach assumes that the population included in the clinical trial is representative of the entire AD population in the EU. Second, the prevalence of VHRDL was assessed using data from general population surveys, corrected for undercoverage using data on the adult per capita consumption of alcohol (obtained from GISAH and details can be found in Table S1 of the supplementary materials) and using the modelling methods of Kehoe and al. (2012).

Assessment of the incidence of alcohol-attributable diseases and injuries among people with VHRDL

A microsimulation model was used to estimate alcohol-attributable 1-year and 10-year disease (liver cirrhosis, pancreatitis, ischemic heart disease, ischemic stroke, haemorrhagic stroke, and pneumonia) and injury risk in patients with AD for a given annual alcohol consumption (François et al., 2014). For these microsimulations, the average volume of ethanol consumed among people with VHRDL was estimated to be 44.5kg per year (122 grams per day) based on the mean consumption of pure alcohol by patients with AD with VHRDL as observed in three recent studies (Laramée et al., 2014).

Estimation of Population-Attributable Fractions

The fractions of diseases attributable to alcohol consumption at very high risk were calculated for cirrhosis, pancreatitis, oral cavity and pharyngeal cancers, colorectal cancer, oesophageal cancer, and haemorrhagic stroke (the sources for these data are outlined in Table S2 of the supplemental material), as data regarding these outcomes were readily available. All population-attributable fractions (PAFs) were estimated using a Levin (1953)-based methodology and using alcohol consumption levels categorized into four broad categories: 0 to 5 (reference group), 6 to 49, 50 to 99, and 100 to 150 grams per day.

The PAFs were estimated by means of a three-step process, first by estimating preliminary study-specific PAFs for each country (α) -specific study and alcohol consumption (i) stratum in accordance with Formula 1, by combining data on the number of patients (C) with the disease of interest (stratified by alcohol consumption) with the prevalence (p) of people in each alcohol consumption stratum (indexed by j). Secondly, study-specific relative risks (RRs) for each alcohol consumption stratum were estimated in accordance with Formula 2, by combining data on the study-specific PAF by study and stratum with prevalence data on alcohol consumption at the country level. Country-level PAFs were then computed by combining study- and alcohol-specific RR data with prevalence data on alcohol consumption at the country level in accordance with Formula 3.

$$SPAF_{\alpha,i} = \frac{C_{\alpha,i} - C_{\alpha,0} \cdot \frac{p_{\alpha,i}}{p_{\alpha,0}}}{\sum_{j=0}^{k} C_{\alpha,i}} \quad \text{(Formula 1)}$$

$$RR_{\alpha,i} = \frac{SPAF_{\alpha,i} + (1 - \sum_{j=1}^{k} SPAF_{\alpha,j}) \cdot p_{\alpha,i}}{p_{\alpha,i}} \cdot \frac{1}{(1 - \sum_{j=1}^{k} SPAF_{\alpha,j})} \quad \text{(Formula 2)}$$

$$PAF_{\alpha,i} = \frac{p_{\alpha,i} * (RR_{\alpha,i} - 1)}{\sum_{j=0}^{k} p_{\alpha,j} * RR_{\alpha,j}} \quad \text{(Formula 3)}$$

Estimation of life expectancy in France

Life expectancy was estimated using the age of onset of drinking at a level of very high risk as follows: (i) 33 years (based on the mean age of onset of AD in recruited patients from the previously-noted clinical trials), and (ii) 47.2 years (based on the mean age of onset of drinking at very high risk levels in recruited patients from the previously-noted clinical trials). Based on these onset ages, the life expectancy for people with VHRDL was then estimated in accordance with Formula 4, by combining data on the number of people with VHRDL in France with data on the number of deaths (D) by disease (d) multiplied by corresponding disease-specific PAFs for VHRD in France. Data on causes of deaths in France were obtained from the CépiDc database (http://www.cepidc.inserm.fr/) (INSERM, 2018).

$$LE_i = \frac{C_i}{\sum_{d=1}^{k} D_d \times PAF_{d,i}} \times \frac{1}{2}$$ (Formula 4)

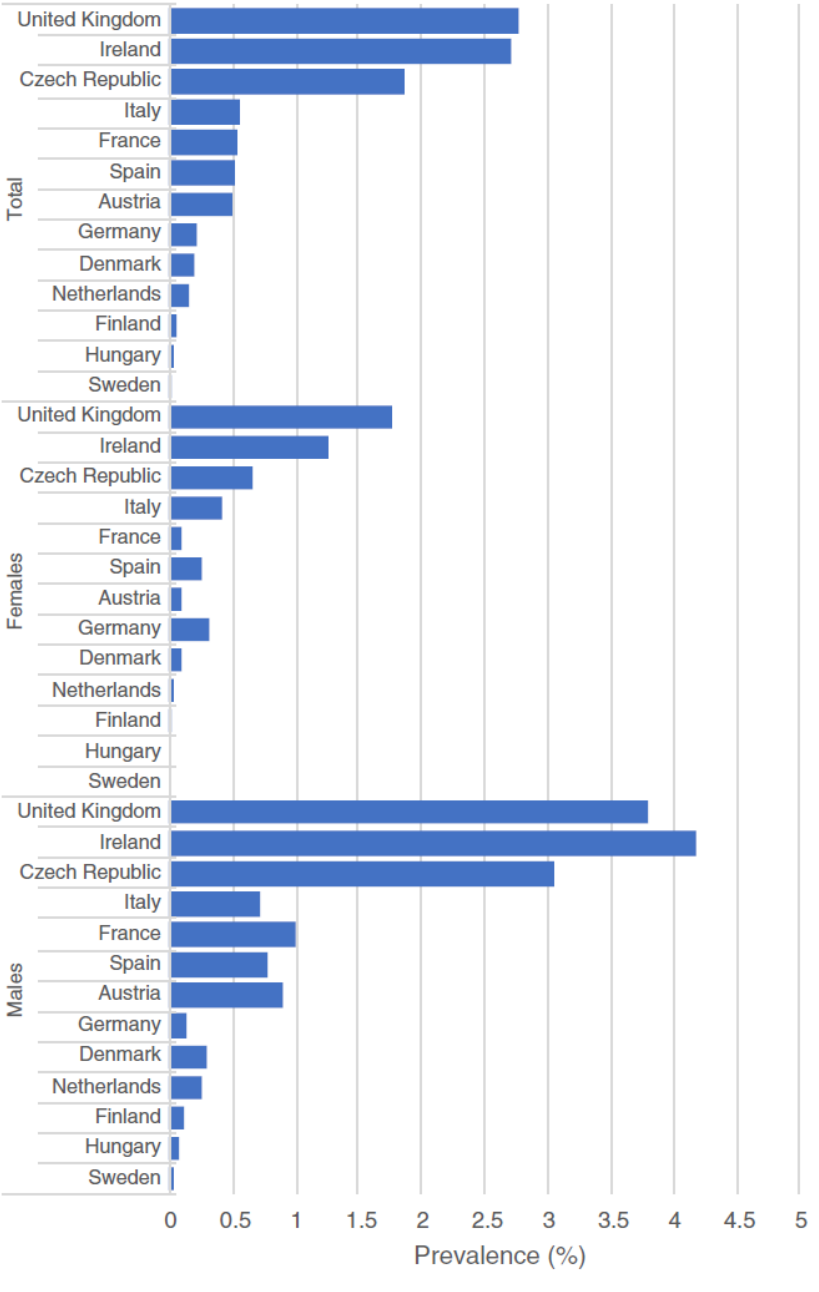
RESULTS

Prevalence and the number of people with VHRDL in the EU

The combination of the number of people with AD in the 13 studied EU countries (10,981,800, representing 3.4% of people 18 to 64 years of age) with the number of patients with AD at VHRDL (21.7%) in the studied clinical trials resulted in an estimate of 2.4 million people 18 to 64 years of age, or 0.74% of this population.

This estimate is also supported by the second approach which relied on data exclusively from the GISAH. Based on this method by Kehoe et al. the prevalence of VHRDL in the 13 European countries was 0.85% among people 15 to 64 years of age corresponding to 2.1 million people (refer to Figure 1). The modelled data indicated large sex-based differences for the prevalence of VHRDL, with the prevalence of VHRDL among men (1.19%) being more than twice that of women (0.50%). Furthermore, the prevalence of VHRDL varied greatly by country, with the prevalence of VHRDL being lowest in Hungary (0.03%), Finland (0.06%), and Sweden (0.02%), and highest in Ireland (2.72%) and the United Kingdom (2.78%).

Figure 1. Prevalence of very high risk drinking among people 15 to 64 years of age in 13 European Union countries



Disease and injury risks among people with VHRDL

The application of the microsimulation model of François et al. (2014) indicated that for people with AD who consume on average 44.5 kg of alcohol per year, there is a resulting risk of 13.5 in 100 of experiencing pneumonia, ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, liver cirrhosis, pancreatitis, traffic injuries, or other injuries in a given year (refer to Table 2). This risk increased to 135.3 per 100 people with VHRDL over a 10-year period indicating a high probability of multiple events (i.e., co-morbidities) per person. The risk of a disease or injury also differed based on the outcome, with the highest probability of non-traffic injuries (5.2 events per 100 people per year), pneumonia (2.1 events per 100 people per year), and ischaemic heart disease (21.6 events per 100 people per year). The relatively lowest risk outcomes were ischaemic stroke (6.9 events per 100 people per year) and haemorrhagic stroke (3.0 events per 100 people per year).

Table 2. Incidence and risk of occurrence over 1-year and 10-year periods for the considered diseases and injuries in an alcohol-dependent population drinking 44.5kg of pure alcohol per year

Disease / injury	Risk of occurrence over a 1 year period per 100 patients	Risk of occurrence over a 10 year period per 100 patients
Pneumonia	2.5	25.3
Ischaemic heart disease	2.2	21.6
Ischaemic stroke	0.7	6.9
Haemorrhagic stroke	0.3	3.0
Liver cirrhosis	1.0	10.2
Pancreatitis	0.9	8.7
Traffic injuries	0.7	7.3
Other injuries	5.2	52.5
Total	13.5	135.3

Disease occurrence attributable to very high risk drinking

The estimation of the number of disease events using data from the clinical trials combined with data from the general population indicated that alcohol consumption higher than 100g per day (i.e., very high risk drinking) was responsible for 53.55% of all liver cirrhosis, 43.75% of all pancreatitis, 41.09% of all oral cavity cancers, 24.79% of all oesophageal cancers, 17.63% of all colorectal cancers, and 9.98% of all haemorrhagic strokes (Table 3). As with the prevalence of VHRDL, the fractions of disease attributable to very high risk drinking also varied by country: for example, the PAF for liver cirrhosis was highest in Ireland (76.42%) and the United Kingdom (74.91%) and lowest in Sweden (6.22%).

The application of the PAFs to the number of deaths in France in 2013 resulted in an estimated 9,832 deaths (representing 21.08% of all deaths) attributable to very high risk drinking, the majority of which were due to alcohol-attributable liver cirrhosis (3,774 deaths), colorectal cancer (1,926 deaths), and oral cavity and pharyngeal cancers (1,556 deaths) (refer to Table 4). This death profile leads to an estimated life expectancy of 47 years of age for patients with AD with VHRDL, based on an age of onset of very high risk drinking of 33 years of age, and an estimated life expectancy of 61 years of age for these same patients, based on an age of onset of very high risk drinking of 47.2 years of age; these life expectancy estimates represent 21 to 35 fewer years than the life expectancy of the general population of France.

Table 3. Deaths attributable to very high risk drinking in France in 2013

Cause of death (ICD-10 code)	Deaths[1]	Deaths attributable to very high risk drinking	Population Attributable Fraction (%) for very high risk drinking
Oral cavity cancer	3,954	1,556	39.34
Colorectal cancer	12,689	1,926	15.18
Oesophageal cancer	3,772	849	22.52
Haemorrhagic stroke	18,314	1,374	7.50
Liver cirrhosis	7,087	3,774	53.25
Pancreatitis	833	353	42.43
Total (conditions studied)	46,649	9,832	21.08

ICD-10 = International Classification of Diseases 10th Edition.
[1] Source: CépiDc (http://www.cepidc.inserm.fr/)

Table 4. Population-attributable fractions for alcohol consumption ≥100g/day

Disease	Austria	Denmark	Finland	France	Ireland	Netherlands	Spain	Sweden	United Kingdom	Mean[1]
Oral cavity and pharyngeal cancer	34.61	20.32	15.52	39.34	63.2	18.12	36.77	4.62	61.13	41.09
Colorectal cancer	12.73	5.95	4.16	15.18	33.14	5.01	13.04	0.92	31.21	17.63
Oesophageal cancer	19.48	10.05	7.37	22.52	42.04	8.88	20.82	1.94	40.06	24.79
Haemorrhagic stroke	6.7	2.64	1.77	7.5	21.3	2.18	6.42	0.36	19.68	9.98
Liver cirrhosis	49.43	30.33	23.12	53.25	76.42	26.5	49.48	6.22	74.91	53.55
Pancreatitis	39.86	22.94	17.65	42.43	65.13	20.45	39.85	5.12	63.19	43.75

[1] Each country was weighted based on the number of cases in each study

DISCUSSION

The relatively small group of approximately 2.4 million people with VHRDL in the 13 EU countries experienced a disproportionately large burden of mortality. Based on findings from François et al. (2014), the risk of occurrence of alcohol-attributable harmful events in alcohol-dependent subjects with very high drinking risk levels was estimated at 13.5%. This extremely high annual number of harmful events indicates that people with AD drinking at very high risk levels will be subject to a substantial number of hospitalizations if their consumption levels are not reduced by interventions (Roerecke et al., 2013), and that it is highly likely that most of these people will be hospitalized for alcohol-attributable diseases or injuries during their lifetime. This assumption is further supported by the fact that individuals with very high risk drinking levels provide 54% of all cirrhosis cases, 44% of all pancreatitis cases, 41% of all oral cavity cancers, and 10% of all haemorrhagic stroke cases. Based on these attributable fractions, the life expectancy of AD patients with VHRDL is estimated to be 47 to 61 years of age, based on age of onset of this behaviour being 21 to 35 years less than the life expectancy of the general population.

The results of this study also emphasize the impact of alcohol at younger ages. Unlike other risk factors, such as tobacco, which primarily affect people older in age, alcohol consumption also affects younger people, and is the top and second-ranked risk factor among people 15 to 49 years of age for deaths and DALYs respectively, outranking dietary risks, occupational risks, smoking, high blood pressure, and high body mass index (Shield and Rehm, 2015). Based on the presented analyses, the impacts of very high risk drinking also disproportionately affect younger people such that the life expectancy of people with VHRDL is less than the age of retirement in most countries.

One limitation of our study is the assumption that in one variant of our calculations, we assumed that the drinking level of the patient sample in the European trial of van den Brink et al. (2014) was representative of the drinking level of people with AD in Europe. We realize, that in different trials different proportions of people with VHRDL can be found, based on recruitment strategies, treatment alternatives in the region and eligibility criteria. As we cannot ascertain this assumption, we introduced a second methodology to estimate the prevalence of people with VHRDL. As the prevalence based on the trial of van den Brink et al. (2014) converged with prevalence estimated via general population modelling, there was probably not much bias resulting from our assumption.

The life expectancy analyses of this study were simplified to ignore latency periods and assume a constant very high risk level of alcohol consumption over

time, starting from different onset dates. For cancers in particular, the mean time lag between the consumption of alcohol and the diagnosis of certain cancers may be 20 years (Holmes et al., 2012). Additionally, we assumed persistence of VHRDL, and this may not be the case for some people with AD where drinking levels fluctuate (e.g. Gual et al., 2009). Despite these limitations, empirical research has corroborated our results that severe AD is linked to large reductions in life expectancy. A recent study analyzed the life expectancy of hospitalized patients diagnosed with AUDs from 1987 to 2006 in Denmark, Finland, and Sweden (1,158,486 person-years studied), and observed that people hospitalized with an AUD had an average life expectancy of 47-53 years of age for men, and 50-58 years of age for women; and died 24-28 years earlier compared to people in the general population (Westman et al., 2015). Similarly, in a recent analysis of French population data based on more than 26 million patients (Schwarzinger et al., 2017), AD was associated with an average age at death of 64.9 years for patients with AUDs, namely 12.2 years younger than other adults without AUDs dying in hospital (10.4 years younger for men and 13.7 years younger for women).

The microsimulation model of François et al. (2014) is limited as it is based only on the selected outcomes of pneumonia, ischaemic heart disease, ischaemic stroke, haemorrhagic stroke, cirrhosis, pancreatitis, and traffic and other injuries. Numerous infections, diseases, and injuries which are also causally related to alcohol consumption were excluded from this model, and also excluded in our study when modelling the burden of disease attributable to very high risk drinking in the 9 EU countries (this also affects the subsequent analysis of the life expectancy for people with VHRDL in France). Alcohol is a necessary cause in 40 three digit ICD-10 code diseases and a component cause in approximately 200 ICD-10 code infections, diseases, and injuries (Rehm et al., 2017; World Health Organization, 2014). Therefore, the presented overall disease risks, health burdens, and life expectancy estimates for people with VHRDL are likely conservative estimates.

The results of this study are also limited as they reflect only the physical and/or mental health harms to the drinker. Indeed, alcohol consumption is also associated with negative socio-economic consequences to the drinker and those around the drinker, to health harms to others (e.g., a drunk driver who is responsible for injury fatalities of others) (Rehm et al., 2012), and to social costs such as lost productivity (Manthey et al., 2016; Rehm et al., 2009). The extent to which very high risk drinking contributes to these broader harms is unknown.

CONCLUSIONS

Based on the substantial mortality and morbidity caused by AD in conjunction with very high risk drinking, this condition should be considered as a life threatening and seriously debilitating disease in accordance with EMA criteria. The WHO considers the reduction of the alcohol-attributable burden of mortality in Europe to be an urgent matter (Shield et al., 2016). Although the risk of all types of alcohol-attributable harms in Europe has recently decreased due to reductions in adult *per capita* consumption, the burden of alcohol-attributable diseases and injuries in this region remains high (Anderson and Baumberg, 2006). Even though the population of people consuming alcohol at a very high risk level is small, these people account for a significant proportion of certain diseases, and, given the burden associated with very high risk alcohol consumption, early evidence-based interventions and effective treatments should be a priority based on their potential impact on the drinker, those within the drinker's social network, and society as a whole (Rehm et al., 2013, 2012).

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CONFLICT OF INTEREST

JG and RP are employees of Debregeas et Associes. KDS declares no conflict of interest.

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CHAPTER 7

Summary and general discussion

INTRODUCTION

Alcohol dependence (AD) is a prevalent mental disorder that is responsible for substantial morbidity and mortality (Rehm et al., 2010). Unfortunately, many AD patients fail to respond to currently available medications for AD (European Medicines Agency, 2010a; van den Brink et al., 2018). Therefore, additional treatment options are needed, preferably with a different mechanism of action than currently available medications. Sodium oxybate (SMO) is such an option that until now has been approved as an oral solution (Alcover®) and available only in Italy and Austria for the treatment of alcohol withdrawal syndrome (AWS) and the maintenance of abstinence in AD patients since 1991 and 1999, respectively (van den Brink et al., 2018). The work presented in this thesis aims to further support the efficacy and safety of SMO in the maintenance of abstinence in AD patients for potential future registration procedures of SMO in the treatment of AD outside Italy and Austria.

OVERALL SUMMARY OF FINDINGS

The approvals of Alcover® in Austria and Italy are based on evidence of clinically relevant positive outcomes from a series of open-label and blinded randomized controlled trials (RCTs) (Addolorato et al., 1999; Caputo et al., 2014, 2007, 2003; Gallimberti et al., 1992, 1989; Leone et al., 2010; Nava et al., 2007, 2006; Nimmerrichter et al., 2002). To expand access to SMO for the treatment of AD in other countries, the existing positive results for the maintenance of abstinence needed to be confirmed by a large phase III trial, a trial exploring the SMO dose-response relationship, and a better understanding of the until now unexplained heterogeneity of SMO treatment effect across and within trials. SMO was well tolerated in the clinical trials and in long-term standard clinical use (Addolorato et al., 2020). However, SMO is the sodium salt of γ-hydroxybutyric acid (GHB) and cases of abuse and diversion of (illicit) GHB have been reported (Addolorato et al., 2009; Németh et al., 2010). Therefore, an abuse/misuse deterrent SMO formulation could further improve the benefit-risk ratio of the compound in the treatment of AD.

In this dissertation, data from a phase IIb RCT (SMO032) that tested the efficacy and safety in the maintenance of abstinence of four doses of an abuse/misuse deterrent SMO granules formulation (Hopveus®) suggested the SMO dose should be adapted based on patient's alcohol consumption at baseline and body weight (Chapter 2). Results of a large phase III international multicentre RCT (GATE 2) confirmed SMO efficacy in the maintenance of abstinence in AD patients (Chapter 3). In addition, significant heterogeneity of the SMO treatment effect across sites was detected in this study and the treatment effect at site level was

negatively correlated with the placebo response at the various sites (Chapter 3). Heterogeneity of the SMO treatment effect and a similar relationship between SMO effect sizes and placebo responses were also found in Chapters 2, 4, and 5 using different data sets and different statistical techniques (interaction tests, subgroup analyses, (network) meta-regression analyses). High baseline AD severity and longer treatment duration were associated with larger SMO effect sizes. This is important since there is an important medical need in the high-severity population due to the severity of the disease (Chapter 6) and the large proportion of patients that fails to maintain abstinence with existing interventions (Chapter 4; Litten et al., 2013). SMO was well-tolerated in the phase IIb as well as in the phase III trial (Chapters 2 and 3). The SMO granules formulation (Hopveus®) showed promising abuse/misuse deterrent properties with no abuse/overdose/misuse/diversion cases reported (Chapter 2).

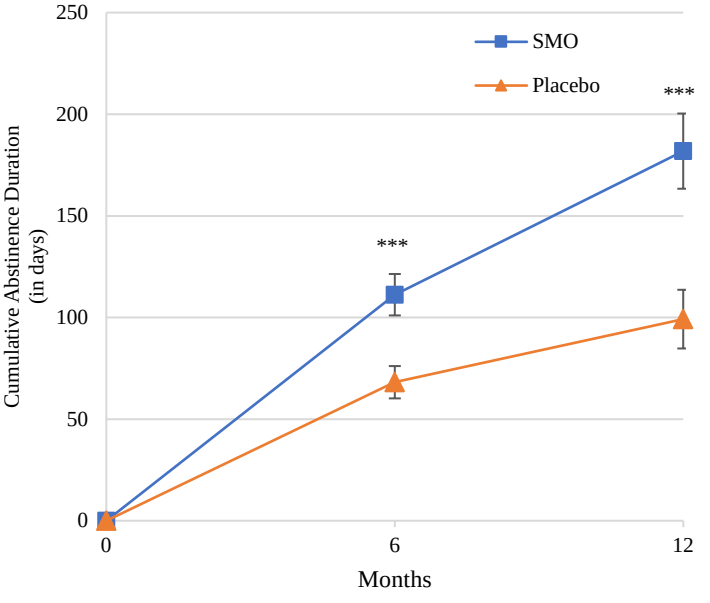
KEY FINDINGS

SMO efficacy in maintenance of abstinence in the phase III GATE 2 study

Chapter 3 presents results of the phase III international, double-blind, placebo-controlled GATE 2 RCT that aimed to confirm the efficacy and safety of SMO (≈50mg/kg/day) in the maintenance of abstinence in AD patients. The study was conducted in accordance with Good Clinical Practices and methods were prespecified in a protocol. The allocation sequence was random, stratified by site, and concealed during the study period. There were no clinically relevant differences in baseline demographic or clinical characteristics between the two groups. Sponsor, investigators, and patients were blind to treatment assignment during the full study period. SMO and placebo oral solutions were identical in appearance and taste.

The study was positive in the prespecified primary analysis of the primary endpoint: SMO showed a statistically significant and clinically relevant higher Cumulative Abstinence Duration (CAD) after 6 months treatment in the intent-to-treat population (Figure 1): adjusted mean (95% confidence interval (CI)) difference +43.1 days (17.6, 68.5), p=0.001.

Figure 1. Adjusted mean CAD over the study period



Bars indicate standard error; ***: $p \leq 0.001$

CAD was measured in accordance with the recommendation from the European guideline for the development of AD treatment (Plinius Maior Society, 1994). A sensitivity analysis using multiple imputation supported SMO efficacy in CAD, suggesting a low risk of bias related to missing data. Furthermore, SMO efficacy in CAD was sustained during the 6-month untreated follow-up period.

In Chapter 5, it was shown that the risk of bias for the results of the primary outcome of this study was considered to be low on the five bias domains of the revised Cochrane risk-of-bias tool for randomized trials (RoB2) (Sterne et al., 2019).

Similarly, an assessment using the GRADE criteria (Guyatt et al., 2011) supports a high evidence quality of SMO efficacy in CAD in the GATE 2 study. The GRADE guidelines provide criteria to rate the evidence quality for a study outcome as either high, moderate, low, or very low. According to these criteria, evidence quality from an RCT is considered to be high when there is no serious risk of bias (see RoB2 above), no serious indirectness (i.e., no major differences between the population, the intervention, or the outcomes measured in the studies and those under consideration in a guideline or systematic review), and no serious imprecision (i.e. clinical action would not differ if the upper versus the lower boundary of the CI represented the truth) (Guyatt et al., 2011). The GATE 2 RCT

recruited 314 AD patients from 11 sites in Austria, Germany, Italy, and Poland. Generalizability of results was supported by a secondary analysis of the primary endpoint using a site level random effect meta-analysis model showing a significant effect of SMO with a point-estimate consistent with the one from the primary analysis. CAD was the primary endpoint recommended by the European guideline for the development of AD treatment at the time GATE 2 was designed (Plinius Maior Society, 1994) as shown by the fact that CAD was utilized as the (co-)primary endpoint in acamprosate trials, including those that were used as pivotal evidence in the registration process of the drug for maintenance of abstinence in the European Union (EU) (Spanagel and Mann, 2005). Results of the prespecified analysis of the primary endpoint were highly significant (p=0.001) and the lower limit (+17.6 days) and the upper limit (+68.5 days) of the 95% CI of the mean difference in CAD were both clinically relevant, supporting no serious imprecision. Therefore, the GATE 2 RCT showed SMO efficacy compared to placebo in CAD after 6 months treatment with a high level of evidence.

Random effect meta-analysis investigating heterogeneity of effect in GATE 2 RCT

In Chapter 3, the role of site in SMO efficacy was tested with a treatment-by-site interaction term in the fixed-effect two-way analysis of variance (ANOVA) and with a site level random effect meta-analysis. To our knowledge, this is the first time that the latter method is used to explore the generalizability of the results in a study for the treatment of AD. The treatment-by-site interaction test in the ANOVA was not significant (p=0.16), but the site level meta-analysis showed significant heterogeneity of SMO treatment effect across sites in the GATE 2 study (I^2=60.8%; p=0.001). Therefore, this site level meta-analysis seems to be more powerful than an interaction test to detect heterogeneity in treatment effect across sites. This is of particular importance since interaction tests generally lack power (sensitivity) to detect heterogeneities in treatment effects that are of potential clinical importance (European Medicines Agency, 2019a) whereas heterogeneity of treatment effect is in fact common in AD trials (Litten et al., 2013). Thus site level meta-analysis can or maybe should be used to explore treatment effect heterogeneity in existing and future RCTs if randomization is stratified by site.

SMO treatment effect: The role of placebo response and its predictors

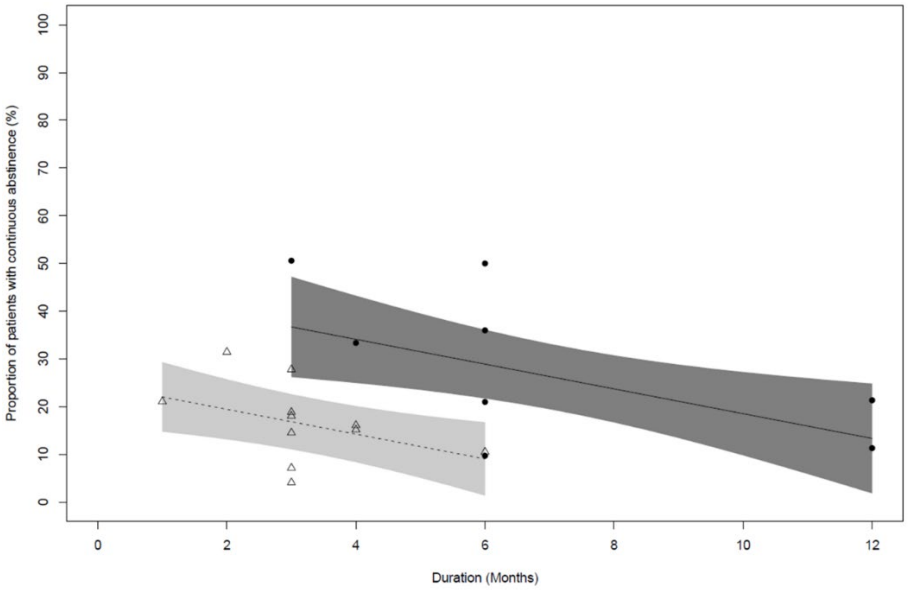
In Chapter 3 (GATE 2 RCT) it was not only shown that treatment effect heterogeneity in CAD across sites was substantial, but also that the estimated SMO treatment effect in CAD at site level was negatively correlated with the placebo response in the sites: treatment effect was smaller in sites with a stronger placebo response. Furthermore, in the phase IIb SMO032 RCT investigating the efficacy of four SMO doses in the maintenance of abstinence in AD patients (Chapter 2), the demonstration of efficacy in the primary endpoint was probably compromised by an unexpectedly high treatment response in the placebo condition: mean 73%, median 92% in the percentage of days abstinent (PDA). It is well-known that studies often fail when the response in the placebo condition is unexpectedly high (European Medicines Agency, 2007). It was therefore important to identify the potential predictors of the placebo response and the potential effect modifiers of SMO. Population severity and treatment duration have been identified as potential predictors of the placebo response and as effect modifiers of several pharmacological interventions for the treatment of AD (Mann et al., 2016; Pierce et al., 2018; van den Brink et al., 2018, 2014, 2013). However, the influence of these factors on SMO efficacy and on the placebo response had not been systematically explored before. In this context, we decided to test the effect of these variables on both the placebo response and SMO efficacy in the maintenance of abstinence in AD patients within and across studies.

Population severity distinguishes heavy drinking patients with <14 days of abstinence before treatment initiation (high-severity population) from other patients (mild-severity population) (Mann et al., 2016; Pierce et al., 2018; van den Brink et al., 2018, 2014, 2013). Treatment duration reflects the planned treatment duration.

In Chapter 4, we systematically tested the effect of population severity and treatment duration on response in terms of the continuous abstinence rate in the placebo condition in relevant RCTs, using meta-regression analysis. A total of 19 placebo-controlled RCTs (with 1,996 placebo-treated patients) directed at the maintenance of abstinence in AD patients were retained in the analysis: 11 trials were assigned to the group of high-severity RCTs and 8 to the group of mild severity RCTs. The continuous abstinence rate in the placebo groups was dependent on population severity ($p=0.004$) and treatment duration ($p=0.017$) and was lower in the high-severity group of studies (16.8% at 3 months) compared to the mild-severity group of studies (36.7% at 3 months). After adjustment for population severity, the placebo response decreased by 2.6% per month of

treatment, e.g., the longer the treatment duration, the lower the placebo response (Figure 2).

Figure 2. Relationship between abstinence rate and treatment duration in high-severity population and mild-severity population (meta-regression)



Circles indicate studies in mild-severity population, and the line shows the regression with 95% confidence band. The triangles show studies in high-severity population and the dotted line shows the regression with 95% confidence band

These findings can improve the efficiency of future drug development for AD. Development of medications for the treatment of AD is challenging and the demonstration of efficacy of treatments approved for this indication is generally based on a mix of positive and negative studies (European Medicines Agency, 2010a; Litten et al., 2012; Witkiewitz et al., 2019). One of the main reasons for these mixed results has been the unpredictable variability of the placebo response in RCTs for AD. In an analysis on 51 naltrexone and acamprosate double-blind RCTs, the placebo response was significantly negatively correlated with the treatment effect size on continuous abstinence rate (Litten et al., 2013).

Therefore, our findings support that future pharmacological RCTs for AD should consider the selection of high-severity patients and/or long treatment durations to lower the placebo effect and its variability. Using these characteristics, the detection of a drug effect (if in fact present) is probably more likely than it would be in an unselected patient population.

Population severity and treatment duration associated with SMO efficacy

In Chapter 2, the moderating effect of population severity and treatment duration on SMO efficacy in the maintenance of abstinence was first investigated in the phase IIb SMO032 RCT using an interaction test and a subgroup analysis conducted in accordance with EMA guideline on exploratory subgroup analysis (European Medicines Agency, 2019a). A significant interaction (p=0.001) was detected between treatment condition and population severity on the PDA, indicating that the treatment effect was dependent on population severity. In the high-severity subpopulation (154 patients), pooled SMO doses showed statistically significant higher PDA (mean difference +15.0%, p=0.02) and continuous abstinence rate (risk difference +18.1%, p=0.04, RR=2.22) compared to placebo. SMO treatment effect in PDA increased and the placebo response decreased with longer treatment duration. SMO did not show any improvement in the mild severity group. The other placebo-controlled RCTs testing SMO efficacy were conducted exclusively in a high-severity or a mild-severity population, making the within trial analysis of the population severity effect irrelevant for these studies.

Given the above results, the effect of population severity and treatment duration on SMO efficacy was then tested across trials using a network meta-regression analysis of eight studies with a total of 1,082 treated AD patients (Chapter 5). The high-severity group of studies was associated with larger SMO effect sizes than the mild-severity group of studies: continuous abstinence rate RR 3.16, p=0.004; PDA +26.9%, p<0.001. For PDA, longer treatment duration was also associated with larger SMO effect size: +11.3% per extra month, p<0.001. Given this interaction effect, SMO efficacy was then explored in each population severity group separately using a network meta-analysis. In the high-severity group, SMO showed benefit: continuous abstinence rate RR 2.91, p=0.03; PDA +16.9%, p<0.001. In the mild-severity group, SMO showed benefit only in PDA for longer treatment duration: +23.9%, p<0.001 (Chapter 5).

These analyses provide data to explain at least some of the heterogeneity of SMO efficacy and may help healthcare providers in the use of SMO for the treatment of AD. Results support the efficacy of SMO independent of treatment duration in high-severity patients and of long-term SMO treatments in mild-severity patients.

SMO dose-response related to baseline level of alcohol consumption

In Chapter 2, an inverted U-shape SMO dose-response relation was found that was influenced by the baseline level of alcohol consumption and body weight in the SMO032 study: the more alcohol consumed at baseline, the higher the SMO dose in mg/kg needed to obtain a positive effect. In the high-severity population, an SMO dose of 60 mg/kg/day had the highest response. 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 the efficacy of SMO in the prevention and treatment of AWS 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 the substitution effect for ethanol had an inverted U-shape function for SMO dose in mg/kg (Colombo et al., 1995; Colombo and Gessa, 2000). Furthermore, 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).

The observed SMO dose-response relation is thus plausible and may help healthcare providers in prescribing an appropriate SMO dose depending on patient's bodyweight and severity at baseline, and in identifying the SMO dose beyond which increases would be unlikely to provide added benefit. Furthermore, the identification of a dose-response gradient is recognized as an important criterion for believing a putative cause-effect relationship (Guyatt et al., 2011). Therefore, the identified dose-response increases the quality level of evidence of SMO efficacy in the maintenance of abstinence.

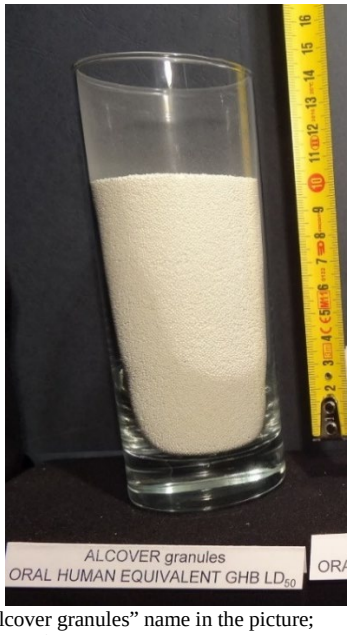
SMO safety profile confirmed

In the GATE 2 and SMO032 studies (Chapters 2 and 3), the adverse event profile of SMO was as expected from previously published trial data and pharmacovigilance studies (Addolorato et al., 2020) and reflects the pharmacological profile of SMO. The most frequently reported adverse events (AEs) were headache, dizziness, nausea, fatigue, and vertigo with dizziness, fatigue and vertigo being more prevalent in patients on higher SMO doses.

In the GATE 2 and the SMO032 studies, the percentage of patients with AEs leading to permanent discontinuation of the study medication was lower in the SMO groups than in the placebo groups, except for the group treated with the highest tested SMO dose (2.25g t.i.d.) for which the percentage in the SMO group was similar to the placebo group. No fatal serious adverse events (SAEs) related to the study medication were reported in the GATE 2 or the SMO032 study. One death was reported in GATE 2 but it was not considered to be related to the study medication: the patient was murdered. The incidence of non-fatal serious AEs was comparable between the SMO and placebo groups in both studies. In the SMO032 study, there were 1,746 cumulative days of concomitant exposure to alcohol and SMO, but no respiratory depression was reported. However, two SAEs (loss of consciousness and discomfort) occurred in one female patient treated with a high SMO dose (2.25g t.i.d. corresponding to 130mg/kg/day) who relapsed 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.

No cases of diversion were reported. The craving for medication was similar in the SMO and placebo groups in both studies. In the GATE 2 study, a total of 154 patients was exposed to SMO and one patient (0.6%) experienced an overdose of SMO (oral solution) that was considered by the investigator to be serious and related to the study medication. In the SMO032 study, a total 408 patients were exposed to SMO and no cases of abuse or overdose were reported, suggesting a better safety profile of the granules formulation thanks to its abuse deterrent properties. 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. This formulation may thus further improve the benefit-risk profile of SMO in the treatment of AD, especially in patients with an increased risk of abuse, i.e., patients with polydrug dependence or severe psychiatric comorbidities (Addolorato et al., 2020).

Figure 3. Dose of SMO granules to be ingested to reach the LD50 oral human equivalent dose



SMO granules presented under "Alcover granules" name in the picture;
LD50: median lethal dose. GHB LD50 found in mice and rats were converted into an oral Human Equivalent Dose (HED) using the US Food Drug Administration methodology (FDA, 2005). To reach this HED LD50 of GHB with granules, 90 sachets of 1.25g SMO would be needed

SMO targets seriously ill patients with an important medical need

SMO was (most) effective in the high severity AD population. This population includes chronic very heavy AD drinkers (>60 g/day of pure alcohol for women and >100g/day for men). There is strong evidence that alcohol-related harms are largely determined by the volume of alcohol consumed, and the risk of disease occurrence increases in an exponential dose–response manner and accumulates over time (Laramée et al., 2014; Rehm et al., 2017; Shield et al., 2013). In Chapter 6, we estimated that chronic very heavy drinkers represent 0.74-0.85% of the general population aged 15 to 64 years in the 13 EU countries that were examined and are responsible for 53.6% of all cases of liver cirrhosis, 43.8% of all cases of pancreatitis, 41.1% of all oral cavity cancers, 24.8% of all oesophageal cancers, 17.6% of all colorectal cancers, and 10.0% of all haemorrhagic strokes. Therefore, AD subjects with a long-term very heavy alcohol consumption have a life expectancy of only 47–61 years, i.e., 21–35 years less than the general

population including “moderate“ drinkers. These results indicate that the health burden of very heavy drinkers – the target population for SMO - is large.

In Chapter 4, the estimated placebo (plus psychosocial support) response in the continuous abstinence rate in the high severity population was 16.8% at 3-month treatment. In AD populations with this level of placebo (plus psychosocial support) response, the existing pharmaceutical interventions (acamprosate and naltrexone) showed an estimated response in continuous abstinence rate of 27.7% (Litten et al., 2013). These data suggest that more than two-thirds of the patients in the high-severity population fail to maintain abstinence with existing interventions.

There is therefore an important and urgent need for additional AD medications, especially in the high-severity population.

LIMITATIONS

The data of the GATE 2 and SMO032 studies presented in the current thesis (Chapters 2 and 3) have been reviewed by the European Medicines Agency (EMA) from 2017 to 2020 in the context of a request to register SMO for the treatment of AD in Europe. The problems and limitations identified by EMA in the GATE 2 and SMO032 studies are discussed below, together with limitations regarding the findings and conclusions on the moderators of the SMO treatment effect and the predictors of the placebo response (Chapters 4 and 5).

The registration procedure for a conditional marketing authorization (CMA) in the EU for Hopveus® ended in April 2020 with a negative conclusion by EMA regarding the benefit-risk balance. Claimed indications were similar to the ones approved for Alcover® in Austria and Italy: treatment of AWS and maintenance of abstinence in AD patients (European Medicines Agency, 2020a). CMAs provide early access to drugs targeting a life-threatening or seriously debilitating disease with an unmet medical need. They are granted based on less comprehensive clinical data than required for an unconditional marketing authorization and when the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required. Therefore, 43% of CMAs granted by EMA from 2006 to 2016 are based on results from phase II studies only without control group, with 1.9 studies per application, and less than 300 patients in total (European Medicines Agency, 2017a, 2017b). In contrast, during the CMA procedure for Hopveus®, the following information was provided to EMA: i) GATE 2 and SMO032 trial data, ii) data of an additional 17 clinical studies from the literature (see General Introduction Chapter), iii) two meta-analyses (N=711 and N=282 patients), iv) preliminary analyses of heterogeneity of SMO efficacy, v) safety data from clinical trials and pharmacovigilance studies, and vi) data on the seriousness of the disease (Chapter

6) and the medical need. The EMA qualified AD as a life-threatening or seriously debilitating disease with an unmet medical need. However, the EMA considered that the efficacy of SMO in the treatment of AWS and the maintenance of abstinence in AD patients was not demonstrated and thus, that the benefit risk of SMO in these indications was negative (European Medicines Agency, 2020a). Regarding the maintenance of abstinence, the EMA considered the following points to be severe limitations compromising the demonstration of SMO efficacy: i) limited efficacy in the GATE 2 study, ii) GATE 2 primary endpoint different from the current standard, i.e., continuous abstinence rate, iii) GATE 2 study duration too short, and iv) insufficient sample size, selection of the patient population, and use of post-hoc analyses for the analysis of efficacy in the high-severity population (European Medicines Agency, 2020a). Based on the data presented in this thesis, we will now evaluate the arguments of the EMA that led to the rejection of the CMA for Hopveus®, thereby also providing a general evaluation of the studies in this thesis.

SMO efficacy in the (pivotal) GATE 2 study

For the primary endpoint of GATE 2 study, both results adjusted for site effects (see Chapter 3) and unadjusted results were submitted to EMA. Unadjusted results showed a significant positive, but relatively small, effect of SMO on the CAD during the 6-month treatment period: unadjusted mean difference +16.5 days, p=0.049. In contrast, results adjusted for site effects showed a highly significant SMO effect with a much larger effect size than the unadjusted results: +43.1 days, p=0.001. Importantly, the GATE 2 protocol specified that site effects should be included in the primary analysis of the primary endpoint and that these interaction effects could be removed from the analyses only if they do not show any significant effect. As explained in Chapter 3, there was significant and important heterogeneity in the treatment effect across sites. However, for unknown reasons, the EMA only considered the unadjusted results for GATE 2 and concluded that “The data presented by the applicant in the pivotal GATE 2 study has demonstrated some limited efficacy in mild severity alcohol dependent patients who are generally treated in an ambulatory setting”. Consequently the EMA considered that data from GATE 2 were not sufficient to establish SMO efficacy in the maintenance of abstinence (European Medicines Agency, 2020a).

Subsequently, both unadjusted results and results adjusted for site effects were submitted to two peer-review journals in 2021 and 2022. The statistical reviewers and the Editors of the two journals rejected the unadjusted results because there was significant heterogeneity of the treatment effect across sites, the unadjusted results were (correctly) considered not meaningful, and the analysis was not compliant with the prespecified analysis in the protocol. Moreover, the International Guideline on statistical principles for clinical trials (ICH E9)

stresses the importance of reporting results in accordance with the prespecified analyses for confirmatory trials (ICH E9, 1998). Therefore, only site-adjusted results were published and they support a statistically significant and clinically relevant effect of SMO in the maintenance of abstinence in AD patients. In addition, some reviewers asked for additional sensitivity analyses to address the risk of bias and results of these analyses were consistent with and thus supported the (robustness of the) treatment effect in the primary analysis.

Therefore, we conclude that the data presented in Chapter 3 support that SMO has demonstrated statistically significant and clinically relevant efficacy in the pivotal GATE 2 study.

GATE 2 primary endpoint

The EMA also criticized the clinical relevance of the GATE 2 primary endpoint, i.e., CAD at end of treatment period, and indicated that it does not capture the recommended primary endpoint in the EMA guideline (European Medicines Agency, 2020a). We disagree with the EMA: as explained in Chapter 3, CAD measures the number of days with no alcohol use for each patient. Therefore, CAD can be conceptualized as a composite endpoint that measures both the continuous abstinence rate (i.e., proportion of patients with a continuous abstinence throughout the treatment period - primary endpoint recommended by the EMA) and the abstinence duration in relapsing patients (important secondary endpoint in EMA guideline). According to ICH E9, composite endpoints can be used as a primary outcome in confirmatory trials as long as the method of combining the multiple measurement is specified in the protocol, and an interpretation of the resulting scale is provided in terms of the size of a clinically relevant benefit (ICH E9, 1998). The CAD computation method was specified in the GATE 2 protocol and was compliant with the recommendation from the European guideline for the development of treatment of AD at that time (Plinius Maior Society, 1994). In GATE 2, SMO efficacy in CAD was explained by a higher continuous abstinence rate as well as a longer abstinence duration in relapsing patients in the SMO group. Therefore, CAD captures the beneficial effect of SMO in the continuous abstinence rate. However, it is acknowledged that, although precise and clinically relevant, CAD is more difficult to interpret than abstinence rate.

In addition, SMO efficacy in continuous abstinence rate is supported by results from published SMO meta-analyses. In a meta-analysis of 4 placebo-controlled RCTs (n=711 patients) and 3 naltrexone-controlled RCTs (n=127 patients), SMO showed statistically significant efficacy in continuous abstinence rate: RR (95% CI) 1.35 (1.05, 1.74) vs. placebo and 1.79 (1.20, 2.68) vs. naltrexone (van den Brink et al., 2018). Similarly, in a recent network meta-analysis including 64

trials and 43 interventions conducted in the total AD population, SMO was significantly more effective than placebo in the continuous abstinence rate: odds ratio (95% CI) 2.31 (1.22 to 4.36). In addition, SMO was better ranked in achieving abstinence than the other medications approved for the maintenance of abstinence in this network meta-analysis (Cheng et al., 2020). As described in Chapter 5, results from another network meta-analysis in the high-severity population also showed SMO efficacy in continuous abstinence rate compared to placebo: RR (95% CI) RR 2.91 (1.11, 7.65).

Therefore, we conclude that CAD is a clinically relevant endpoint which also measures continuous abstinence rate and SMO has shown efficacy in continuous abstinence rate and in abstinence duration in relapsing patients.

GATE 2 study duration

The EMA considered the duration of the GATE 2 study to be too short (European Medicines Agency, 2020a). The recommendation in the EMA guideline is an overall duration of confirmatory trials of 12 to 15 months. That means 3 to 6 months active treatment in relapse prevention trials followed by a medication-free follow up until 12 to 15 months after randomization (European Medicines Agency, 2010a, 2010b). The GATE 2 study included a 6-month active treatment period followed by a 6-month medication-free period and thus a total study duration of 12 months. The GATE 2 study duration was thus (largely) compliant with the recommendation of the EMA guideline.

SMO efficacy only in high-severity AD population

As the data from the GATE 2 study (conducted in a mild severity population) were considered by EMA to be insufficient to establish SMO efficacy in the maintenance of abstinence, the EMA reviewed the data from studies conducted in the high-severity population and stated that (European Medicines Agency, 2020a):

- "*Efficacy in a severe (H/VHRDL population) was only evaluated in a post hoc analysis of a minority of subjects in phase 2b study SMO032/10/03 over three months. Of note, no benefit was shown for SMO in the population with mild severity in this study."*
- "*Whilst a higher placebo response in subjects with mild severity alcohol dependence and the short duration of treatment (3 months) may have contributed to the negative outcome of SMO032/10/03 and it is noted that there have been similar reports in the literature, the outcome of these analyses can only be considered to be hypothesis generating*"

- *"The optimal doses identified for this [severe] population was also determined by post hoc analysis. […] there is uncertainly around the characterisation of optimal dose of SMO, the method of its determination and the data supporting the plausibility of the dose response relationship."*
- *"In the opinion of the CHMP the post hoc analyses presented by the applicant regarding the impact of population severity, placebo effect, duration of treatment and determination of optimal dose are hypothesis generating and cannot be considered to be confirmatory of a treatment effect in a H/VHDRL subpopulation".*

Effect of population severity and treatment duration on SMO efficacy

In Chapter 5, we tested the effect of population severity and treatment duration on SMO efficacy across various RCTs using a network meta-regression analysis. Eight studies (1,082 treated AD patients) were included in the analysis: four studies (326 patients) in the high-severity group and four studies (756 patients) in the mild-severity group of studies. Results showed that high-severity population and longer treatment duration were significantly associated with larger SMO effect sizes. SMO efficacy in the maintenance of abstinence was seen in high-severity populations and, in mild-severity populations, with long-term treatments (i.e., ≥ 6 months). The placebo response was much lower for a 6-month than for a 3-month treatment duration in the mild-severity group (mean PDA 37.9% vs. 87.2%). These data reconcile the seemingly conflicting results in mild severity populations: due to a too short (i.e., 3 months) treatment duration (and thus a very high placebo response), no SMO benefit was observed in the SMO032 mild severity subgroup; in contrast, thanks to a longer (i.e., 6 months) treatment period (and thus a much lower placebo response), SMO efficacy was shown in the GATE 2 study that was conducted exclusively in a mild severity population. It should be noted, however, that this network meta-regression analysis investigated differences between studies and individuals were not randomized to go in one trial or another. Hence, this analysis is observational with a risk of bias by confounding, chance findings, and aggregation bias, especially when the sample of studies retained is relatively small compared to the number of covariates/moderators tested (Higgins et al., 2022). To address these risks, it is important to assess the reliability and validity of the findings of this network meta-regression analysis. The EMA and the Cochrane provide criteria to reduce the risk of false causal relationships in meta-regression analyses and to assess the credibility and the plausibility of exploratory subgroup findings (European Medicines Agency, 2019a; Higgins et al., 2022). In Chapter 5, we provided data supporting the fulfilment of all EMA and Cochrane criteria for the credibility and the plausibility of our findings and causal inferences: i) SMO showed efficacy in

the whole study population in GATE 2 study as well as in meta-analyses conducted in the total AD population; ii) the definition of the selected subgroups is based on literature; iii) a pharmacological rationale of the difference of treatment effect between subgroups exists; iv) the difference of efficacy between subgroups was clinically important and statistically significant and the treatment effect in the high-severity was larger than in the mild-severity group, v) the effects of population severity and treatment duration on SMO efficacy were observed within and across trials and are supported by external evidence from trials with other AD medications; vi) the protocol for this review was registered in PROSPERO. We, therefore, conclude that Chapter 5 presents data supporting a probable causal relationship between the tested covariates (population severity and treatment duration) and the SMO treatment effect and thus addresses the critical commentary of the EMA on this topic. Moreover, some years ago, nalmefene was registered by EMA for the reduction of alcohol use in high-severity AD patients based on post-hoc analyses and without a confirmatory trial in severe AD patients only (European Medicines Agency, 2012; Mann et al., 2016; van den Brink et al., 2014, 2013).

Effect of population severity and duration of treatment on placebo response

To address the concern raised by the EMA, we have systematically tested the effect of population severity and treatment duration on the placebo response in maintenance of abstinence using a meta-regression analysis including 19 RCTs (Chapter 4). Results showed that high-severity population and longer treatment duration were significantly associated with lower placebo responses in studies directed at maintenance of abstinence in AD patients. However, and as stated above, this meta-regression analysis is observational by nature and the reliability of the findings should be assessed with the EMA and the Cochrane criteria. Therefore, data were provided in Chapters 4 and 5 to support the fulfilment of the (relevant) EMA and Cochrane criteria: i) the difference of placebo response between subgroups was clinically important and statistically significant and the placebo response in the high-severity was lower than in the mild-severity group, ii) the effects of population severity and treatment duration on the placebo response have been observed within and across trials, iii) the predicted placebo responses for each population severity and by treatment duration based on this meta-regression were consistent with the placebo response measured in studies that were not part of the 19 RCTs retained in the analysis, i.e,. the "validation set" composed of SMO032 high- and mild-severity subgroups, GATE 2 study, study by Gallimberti et al. (1992), and study by Müller et al. (2015). These data strengthen the findings of this meta-regression analysis and thus a probable causal relationship between the tested covariates (population severity and treatment

duration) and the placebo response in the maintenance of abstinence seems to exist.

Determination of the optimal SMO dose

According to International Guideline on dose-response (ICH E4), identification of a dose-response relation is not mandatory for drug registration and approval based on data from studies using a fixed single dose or a defined dose range (but without valid dose-response information) might be appropriate where benefit from a new therapy in treating or preventing a serious disease is clear (ICH E4, 2019). Nevertheless, ICH E4 stresses the importance of analysing the entire clinical database for identification of a dose-response relation, even if the analyses can only yield principally hypotheses, not definitive conclusions (ICH E4, 2019).

In this context, exploratory analyses of the SMO032 study have been conducted (Chapter 2) and they support an adjustment of the SMO dose based on the level of alcohol consumption at baseline and body weight: the more alcohol consumed at baseline, the higher the SMO dose in mg/kg should be administered. In the high-severity population, the SMO dose of 60mg/kg/day had the highest response.

In Chapter 2, we discussed the fulfilment of the EMA criteria for the credibility and plausibility of the SMO dose-response findings (European Medicines Agency, 2019a). Results showed that this dose-response is consistent with the mechanism of action of SMO and is supported by preclinical and clinical data. In addition, the double-blind placebo controlled RCT by Gallimberti et al. (1992) testing the efficacy of SMO 50mg/kg/day in a high severity population showed evidence of SMO efficacy with a similar effect size as the 60mg/kg/day dose in the SMO032 study. The posology approved for Alcover® in the maintenance of abstinence in Italy and Austria is 50mg/kg/day and no safety concerns were reported in the pharmacovigilance database (Addolorato et al., 2020). Finally, all tested SMO doses in clinical trials (i.e., up to 2.25g t.i.d. representing 96mg/kg/day for 70kg bodyweight) were well-tolerated. We, therefore, feel that the dose-selection is well-documented and the criticism of EMA on this topic has little weight in the risk-benefit balance of SMO. However, to address the limitations of the dose-response findings and since no safety concerns were reported with these doses, SMO treatment could be initiated with a dose of 50mg/kg/day and increased to 60mg/kg/day in case of insufficient treatment response in high-severity patients.

FUTURE DIRECTIONS

It would be of interest to explore the effect of population severity and treatment duration on other pharmacological compounds that have been tested in the treatment of AD using a large-scale network meta-regression analysis and to compare the relative efficacy of these compounds (including SMO) according to these covariates using subgroup network meta-analyses.

To provide further data on the clinical relevance of SMO benefit, the cost-effectiveness and the public health benefit of SMO in the maintenance of abstinence in AD patients could be estimated with a Markov model (Laramée et al., 2014).

Although the available data demonstrate an effect of SMO in the maintenance of abstinence, the precision of SMO effect size in each population severity group could be further improved and the causal relationship between population severity and SMO efficacy could be further established with the conduct of additional RCTs (with randomization stratified by population severity, for instance).

Data support an alcohol mimicking effect of SMO. However, the mechanism of action of SMO in AD has not yet been fully explained (Keating, 2014). The neuropsychopharmacological signature of SMO appears to be unique with effects resembling those observed for ethanol and benzodiazepines, with a distinct difference regarding an enhancing effect of SMO on conflict monitoring (Dornbierer et al., 2019). SMO mechanisms of action could be further explored to improve the characterization of the SMO efficacy and safety profile. Indeed, other subgroupings, e.g., according to genetic, neurobiological, and other clinical features, might also be important effect modifiers of SMO (Lesch et al., 2020). They need to be further investigated to improve precision medicine for AD patients.

In this respect, a pilot study showed promising efficacy data of the combination of SMO and naltrexone in the maintenance of abstinence in AD patients (Caputo et al., 2007). The efficacy and safety of this combination should be further explored for patients not responding to either NTX or SMO alone.

Similarly, an open study investigated the effect of greater fractioning of SMO (50mg/kg/day) dose in the maintenance of abstinence in 154 AD patients not responding to the usual three SMO administrations per day. Results showed that non-responder subjects to the conventional fractioning of SMO seemed to benefit from the greater fractioning of the drug (same daily SMO dose but divided in six administrations) (Addolorato et al., 1998). The efficacy and safety of this greater fractioning should be further explored for patients not responding to conventional fractioning of SMO. At the same time, such a frequent dosing schedule may

reduce the clinical usefulness of the medication and an alternative solution could be the development of a long-acting SMO formulation that reduces the frequency of administration as is currently the case with some opioid agonists in the treatment of opioid dependence (e.g., long-acting buprenorphine: Chappuy et al., 2020)

Data support an improved safety profile of the abuse/misuse deterrent granules SMO formulation compared to the oral solution. The safety of this granules formulation could be further studied in patients at risk of abuse, i.e., patients with polydrug dependence or severe psychiatric comorbidities (Addolorato et al., 2020).

SMO is not contraindicated for AD patients with hepatic impairment (Child-Pugh A to C), but the SMO dose should be halved in this patient population (European Medicines Agency, 2021a; Ferrara et al., 1996; van den Brink et al., 2018). The effectiveness and the safety of SMO in the maintenance of abstinence could be tested in AD patient with serious hepatic impairment.

GENERAL CONCLUSION

The work in this thesis offers a clinical package with i) results of a phase III study confirming previous smaller studies on the efficacy of SMO in the maintenance of abstinence in AD patients, ii) data of additional RCTs and network meta-analyses providing further evidence of SMO efficacy in this indication, iii) results of within and across trial analyses to explain the heterogeneity of SMO efficacy, indicating that high-severity AD patients are the best candidates for the treatment with SMO, iv) additional safety data confirming that SMO in the treatment of AD is well-tolerated, v) promising safety results of the new abuse/misuse deterrent granules SMO formulation (Hopveus®).

This dissertation also provides data to address the concerns raised by EMA during its evaluation of the SMO clinical trials as well as data supporting that SMO targets a serious condition with an important need for additional medications, especially in the high-severity population.

Therefore, the work in this thesis can be used to characterize SMO efficacy, safety, and benefit-risk in the maintenance of abstinence in AD patients in future potential registration procedures of SMO in the treatment of AD outside Italy and Austria. In this respect, it is important to remind that SMO has been used for decades in these two EU countries in the treatment of AWS and in the maintenance of abstinence in more than 300,000 AD patients. The EMA has been reviewing the benefit-risk of Alcover® on a yearly basis since 2016 and has considered it to be positive each year from 2016 to the last assessment in 2022 (European Medicines Agency, 2022, 2021b, 2020b, 2019b, 2018, 2017c, 2016).

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English resume

Alcohol dependence (AD) is generally defined as a chronic (relapsing) disease notably characterized by craving, impaired control over drinking, tolerance and withdrawal, alcohol related damage and a clear association with continued high alcohol consumption. AD affects 3.4% of the general population aged 18-64 years in the European Union (EU) and is responsible for substantial morbidity and mortality. AD treatment programs can include the treatment of alcohol withdrawal syndrome (AWS) followed by a maintenance of abstinence intervention, including both psychological and pharmacological treatments. Unfortunately, many AD patients fail to respond to currently available medications for the maintenance of abstinence and none is also effective in the treatment of AWS (**Chapter 1**). Therefore, additional pharmacological treatments are needed, probably including sodium oxybate (SMO).

SMO is the sodium salt of γ-hydroxybutyric acid (GHB). SMO has an alcohol-mimicking effect on the central nervous system and oral SMO 50mg/kg/day has shown efficacy in the treatment of AWS and/or in the maintenance of abstinence in AD patients in 10 randomized controlled trials (RCTs) and in three meta-analyses. SMO as an oral solution has thus been approved in Italy and Austria for these indications since 1991 and 1999, respectively. However, for the maintenance of abstinence, no phase III trial was conducted to confirm these positive results. Moreover, the studies for the maintenance of abstinence did not investigate the sustainability of the SMO effect after treatment discontinuation. Last, unexplained heterogeneity of SMO treatment effect was identified across these studies. Heterogeneity of treatment effect is not specific to SMO and the approval of other medications for the treatment of AD is based on a mix of positive and failed studies with substantial heterogeneity of treatment effect. A meta-regression of 51 RCTs showed that the effect size of these medications was significantly negatively correlated with the placebo response. Interestingly, population severity and treatment duration have been identified recently as potential predictors of the placebo response and potential effect modifiers of these medications for the treatment of AD. Population severity distinguishes heavy drinking AD patients with <14 days of abstinence before treatment initiation (high-severity population) from other AD patients (mild-severity population). Treatment duration reflects the planned treatment duration. However, the effect of these potential moderators on SMO efficacy in the maintenance of abstinence had not been tested (**Chapter 1**).

Regarding tolerability and safety, SMO oral solution in the treatment of AD was well-tolerated both in clinical trials and in standard clinical use in Italy and Austria. However, cases of abuse and diversion of (illicit) GHB have been reported (**Chapter 1**).

Therefore, to expand access to SMO in the treatment of AD in other countries via approval of SMO for this indication by competent regulatory authorities, this thesis has five aims (**Chapter 1**):

i) to test the efficacy and safety of SMO in the maintenance of abstinence in AD patients in a large confirmatory RCT,
ii) to investigate the SMO dose-response relationship in the maintenance of abstinence in AD patients in a large RCT,
iii) to test the safety of a new SMO oral granules formulation with abuse/misuse deterrent properties,
iv) to systematically test the effect of population severity and treatment duration on placebo response and on SMO efficacy in the maintenance of abstinence in AD patients, and
v) to analyse the alcohol-attributable morbidity and mortality in the patient population where SMO seems to be (most) effective.

To confirm the efficacy and safety of SMO (≈50mg/kg/day) in the maintenance of abstinence, a large phase III double-blind, placebo controlled RCT (GATE 2) was conducted in 314 AD patients from 11 sites in 4 EU countries (**Chapter 3**). The study was conducted in accordance with Good Clinical Practices and methods were prespecified in a protocol. Treatment duration was 6 months followed by a 6-month medication-free period. The primary endpoint was the cumulative abstinence duration (CAD) during the 6-month treatment period. Secondary endpoints included CAD during the 12-month study period. CAD measures the number of days with no alcohol use for each patient. The study was positive in the prespecified primary analysis of the primary endpoint: SMO showed a statistically highly significant and clinically relevant higher CAD after 6 months treatment: adjusted mean difference +43.1 days. The robustness of this result was supported by various sensitivity analyses that all showed a significant effect of SMO with similar point-estimates. Furthermore, SMO efficacy in CAD was sustained during the 6-month untreated follow-up period (**Chapter 3**). The risk of bias for the results of the primary outcome of this study was considered to be low (**Chapter 5**). An assessment using the GRADE criteria supports a high evidence quality of SMO efficacy in CAD in this study (**Chapter 7**).

Importantly, the GATE 2 primary endpoint differs from the endpoint currently recommended by the European Medicines Agency (EMA) for phase III trials which is the continuous abstinence rate (i.e., proportion of patients with a continuous abstinence throughout the treatment period). However, CAD can be conceptualized as a composite endpoint that measures both the continuous abstinence rate and the abstinence duration in relapsing patients. SMO efficacy in CAD was explained by a higher continuous abstinence rate as well as a longer abstinence duration in relapsing patients in the SMO group (**Chapter 3**). Therefore, these data support that SMO (≈50mg/kg/day) has demonstrated

statistically significant and clinically relevant efficacy in GATE 2 with a high evidence quality.

The SMO dose-response relation was investigated in a phase IIb international, double-blind, placebo-controlled RCT (SMO032) in 509 AD patients that tested the efficacy and safety in the maintenance of abstinence of four doses of an abuse/misuse deterrent SMO formulation using SMO-granules instead of an SMO-solution (**Chapter 2**). Exploratory analyses showed a dose-response relationship between SMO and alcohol use outcomes that was influenced by the level of baseline alcohol consumption and the patient's body weight: the more alcohol consumed at baseline, the higher the SMO dose in mg/kg needed to be administered for a positive effect. In heavy drinking AD patients, an SMO dose of 60mg/kg/day had the best response (**Chapter 2**). This dose-response is consistent with the pharmacology of SMO and the dose-response observed in preclinical studies. Its role as a substitute for alcohol is supported by efficacy of SMO in the treatment of AWS in several trials and in meta-analyses and by clinical studies which showed similar effects between ethanol and SMO. As this dose-response is based on exploratory analysis and since no safety concerns were reported with these doses, SMO treatment could be initiated with a dose of 50mg/kg/day and increased to 60mg/kg/day in case of insufficient treatment response in heavy drinking AD patients (**Chapter 7**).

Heterogeneity of SMO treatment effect was identified within both the GATE 2 and the SMO032 RCTs. In the GATE 2 RCT (**Chapter 3**), a significant and substantial heterogeneity of treatment effect on CAD across sites was identified. The estimated SMO treatment effect in CAD was larger in sites with a lower placebo response. In the SMO032 RCT (**Chapter 2**), the demonstration of efficacy in the primary endpoint, i.e., percentage of days abstinent (PDA), was probably compromised by an unexpectedly high placebo response (mean 73%) that was much higher than the placebo response in the GATE 2 study (mean 38%). Overall, these data suggest a relation between the SMO treatment effect and the placebo response. Hence, it was of interest to explore the effect of population severity and treatment duration on both the placebo response and the SMO treatment effect.

In **Chapter 4**, the effect of population severity and treatment duration on the placebo response in continuous abstinence rate was systematically tested in 19 placebo-controlled RCTs (with 1,996 placebo-treated patients) directed at the maintenance of abstinence in AD patients (regardless of the tested medication), using meta-regression analysis. The continuous abstinence rate in the placebo groups was significantly dependent on population severity and treatment duration and was lower in the high-severity group of studies compared to the mild-severity group of studies and in studies with longer versus a shorter planned treatment duration. Therefore, the detection of a drug effect (if in fact present) is probably

more likely in the high-severity population. These findings can improve the efficiency of future drug development for AD.

We then investigated the moderating effect of population severity and treatment duration on SMO efficacy in the maintenance of abstinence within trials. In the SMO032 RCT (**Chapter 2**), a subgroup analysis showed significant and clinically relevant SMO efficacy in the high-severity population in both continuous abstinence rate and PDA probably due to a lower placebo response in this severe subgroup. The SMO treatment effect increased, and the placebo response decreased with longer treatment duration. SMO did not show any improvement in the mild severity group probably due to a very high placebo response, leaving almost no room for improvement for the medication. The other placebo-controlled RCTs testing SMO efficacy were conducted exclusively in a high-severity or a mild-severity population, making the within trial analysis of the population severity effect irrelevant for these studies.

In **Chapter 5**, the effect of population severity and treatment duration on SMO efficacy was tested across trials using a network meta-regression analysis of eight studies with a total of 1,082 treated AD patients. The high-severity group of studies was associated with significantly larger SMO effect sizes than the mild-severity group of studies in both continuous abstinence rate and PDA. For PDA, longer treatment duration was also associated with larger SMO effect size. Given these interaction effects, SMO efficacy was then explored in each population severity group separately using a network meta-analysis. In the high-severity group, SMO showed significant benefit in both continuous abstinence rate and PDA with large effect sizes. In the mild-severity group, SMO showed significant benefit only in PDA for longer treatment duration.

These meta-regressions and subgroup analyses provide data to explain heterogeneity of SMO efficacy. However, the presence of (residual) bias and/or confounding cannot be excluded in meta-regression analysis and, therefore, we provided data supporting the EMA and Cochrane criteria for the credibility and plausibility of exploratory subgroup findings/meta-regressions. Based on these findings we believe that there probably is a causal relationship between population severity and treatment duration and the SMO treatment effect. This knowledge may help healthcare providers in the use of SMO for the (personalised) treatment of AD (**Chapter 5**).

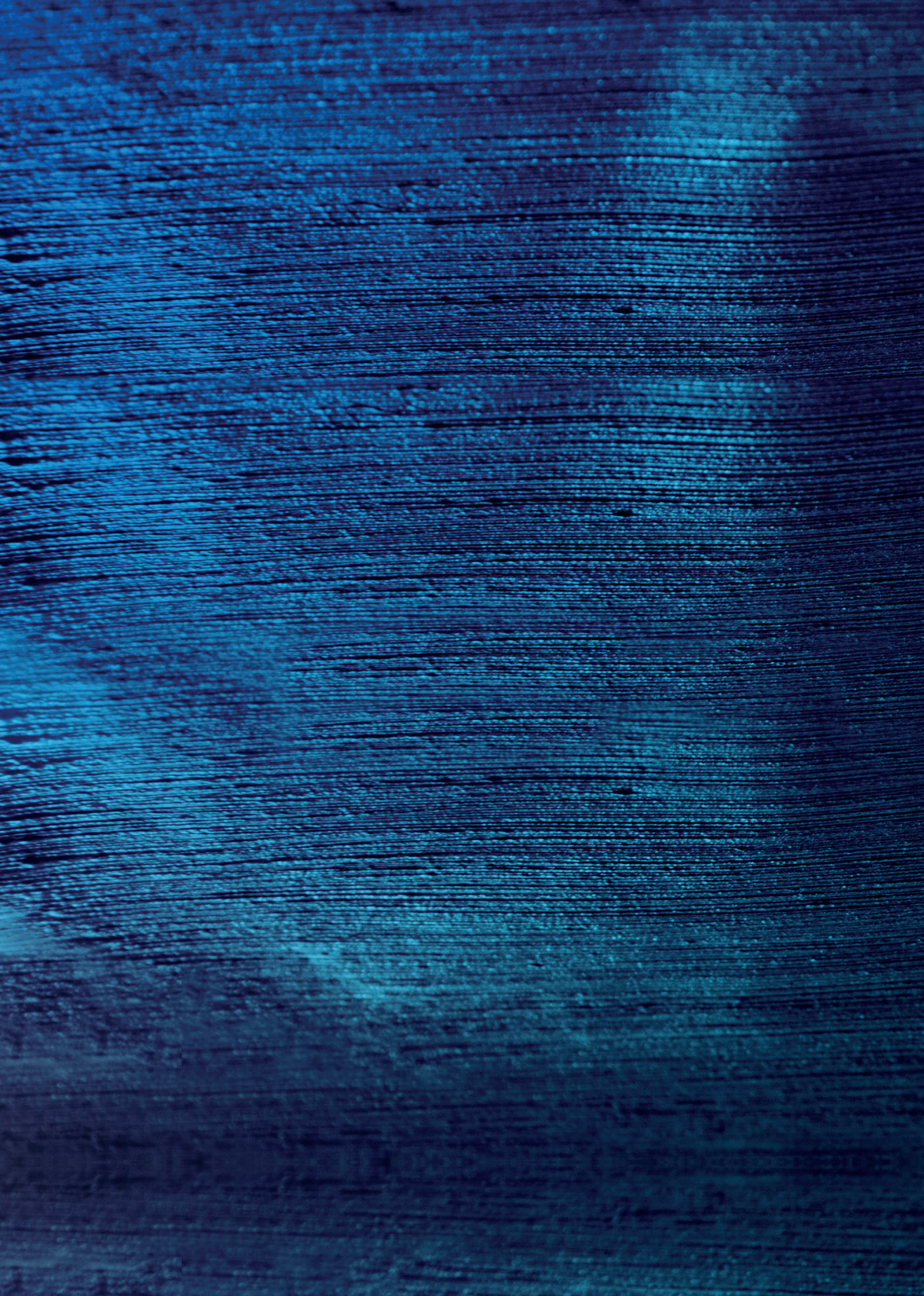
SMO appears to be (most) effective in the high-severity population which include very heavy drinking AD patients. In **Chapter 6**, we estimated that despite affecting “only” 0.74-0.85% of the general population aged 15 to 64 years, very heavy drinkers are responsible for a substantial part of the alcohol-attributable morbidities and have a life expectancy of only 47–61 years. In **Chapter 4**, data suggest that more than two-thirds of the patients in the high-severity population

fail to maintain abstinence with existing interventions (apart from SMO), indicating an important need for additional effective interventions in this patient population.

In the GATE 2 and SMO032 studies, SMO was well-tolerated. The most frequently reported adverse events (AEs) were headache and dizziness. No fatal serious AEs related to the study medication were reported in these studies and the incidence of non-fatal serious AEs was comparable between the SMO and placebo groups. The craving for medication was similar in the SMO and placebo groups in both studies. No cases of diversion were reported in both studies. No cases of abuse or overdose were reported with the new abuse/misuse deterrent SMO granules formulation. One patient (0.6%) experienced an overdose of SMO with the oral solution, suggesting a better safety profile of the SMO granules formulation (**Chapters 2 and 3**).

In **Chapter 7**, future directions have been proposed notably with the investigation of the effect of population severity and treatment duration on efficacy of other pharmacological compounds, a cost-effectiveness analysis of SMO in the treatment of AD, and further studies investigating the efficacy and safety of SMO in AD patients with hepatic impairment.

This dissertation also provides data to address the concerns raised by EMA during its evaluation of the SMO clinical trials from 2017 to 2020 that ended with a negative decision about the approval of SMO in the EU. The work presented in this thesis offers a clinical package that supports efficacy and positive benefit-risk of SMO in the maintenance of abstinence in AD patients and might be used in future registration procedures (**Chapter 7**).



Nederlandse samenvatting

Alcoholafhankelijkheid (AA) wordt doorgaans gedefinieerd als een chronische (recidiverende) ziekte die met name wordt gekenmerkt door hunkering, verminderde controle over het drinken, tolerantie en ontwenning, alcoholgerelateerde schade en een duidelijk verband met langdurig fors alcoholgebruik. AA komt voor bij 3,4% van de algemene bevolking van 18-64 jaar in de Europese Unie (EU) en is verantwoordelijk voor aanzienlijke morbiditeit en mortaliteit. Behandelprogramma's voor AA bestaan uit behandeling van het alcoholonttrekkingssyndroom (AOS) gevolgd door een interventie gericht op het voorkomen van terugval, waarbij het zowel psychologische als farmacologische behandelingen kan gaan. Helaas reageren veel AA-patiënten niet op de thans beschikbare geneesmiddelen gericht op het handhaven van abstinentie en is geen van die geneesmiddelen ook nog effectief bij de behandeling van het AOS (**hoofdstuk 1**). Daarom zijn aanvullende farmacologische behandelingen nodig, waaronder waarschijnlijk natriumoxybaat (SMO).

SMO is het natriumzout van γ-hydroxyboterzuur (GHB). SMO heeft een alcoholachtige werking op het centrale zenuwstelsel en orale SMO 50mg/kg/dag is in 10 gerandomiseerde gecontroleerde onderzoeken (RCT's) en in drie meta-analyses werkzaam gebleken bij de behandeling van AOS en/of het voorkomen van terugval bij AA-patiënten. SMO als orale oplossing is in Italië en Oostenrijk voor deze indicaties goedgekeurd sinds respectievelijk 1991 en 1999. Voor de indicatie “behoud van abstinentie” werd echter nog geen fase III-onderzoek uitgevoerd om deze positieve resultaten te bevestigen. Bovendien onderzochten de studies voor het behoud van abstinentie niet de duurzaamheid van het effect van SMO na het stopzetten van de behandeling. Ten slotte werd in deze studies een onverklaarde heterogeniteit van het SMO-behandeleffect vastgesteld. Heterogeniteit van het behandeleffect is niet specifiek voor SMO en de goedkeuring van andere geneesmiddelen voor de behandeling van AA is meestal gebaseerd op een mix van positieve en negatieve studies met aanzienlijke heterogeniteit van behandeleffect tussen de studies. Uit een meta-regressie van 51 RCT's bleek dat de effectgrootte van medicijnen tegen AA significant negatief gecorreleerd was met de placeborespons. Interessant is dat de ernst van de populatie en de duur van de behandeling onlangs werden geïdentificeerd als potentiële voorspellers van de placeborespons en waarschijnlijk potentiële effectmoderatoren van deze geneesmiddelen tegen AA zijn. De populatie-ernst onderscheidt zwaar drinkende AA patiënten met <14 dagen abstinentie voor aanvang van de behandeling (groep met hoge ernst) van andere AA patiënten (groep met milde ernst). Bij behandelduur gaat het in de onderzoeken om geplande behandelingsduur. Het effect van deze potentiële moderatoren op de doeltreffendheid van SMO bij het handhaven van abstinentie was echter nog niet onderzocht (**hoofdstuk 1**).

Wat tolerantie en de veiligheid betreft, werd de orale oplossing van SMO voor de behandeling van AA zowel in klinische studies als bij standaard klinisch gebruik in Italië en Oostenrijk goed verdragen. Er zijn echter gevallen van misbruik en doorverkoop van (illegale) GHB gemeld (**hoofdstuk 1**).

Om de kans op toegang tot SMO bij de behandeling van AA in andere landen te vergroten is goedkeuring van SMO voor deze indicatie door het Europees Geneesmiddelenbureau (EMA) nodig en daarom heeft dit proefschrift de volgende vijf doelstellingen (**hoofdstuk 1**):

i) Testen van de werkzaamheid en veiligheid van SMO bij het handhaven van abstinentie bij AA-patiënten in een grote bevestigende RCT,
ii) Onderzoeken van de dosis-responsrelatie van SMO bij het behoud van abstinentie bij AA-patiënten te onderzoeken in een grote RCT,
iii) Testen van de veiligheid van een nieuwe formulering van SMO voor oraal gebruik die het moeilijk maakt om het middel te misbruiken of door te verkopen,
iv) Systematisch testen van het effect van de ernst van de populatie en de duur van de behandeling op de placeborespons en op de werkzaamheid van SMO bij het handhaven van abstinentie bij AA-patiënten, en
v) Analyseren van de aan alcohol toe te schrijven morbiditeit en mortaliteit in de patiënten-populatie waar SMO (het meest) effectief lijkt te zijn.

Om de werkzaamheid en veiligheid van SMO (≈50mg/kg/dag) bij het behoud van abstinentie te bevestigen, werd een grote fase III dubbelblinde, placebogecontroleerde RCT (GATE 2) uitgevoerd bij 314 AA-patiënten op 11 locaties in 4 EU-landen (**hoofdstuk 3**). De studie werd uitgevoerd in overeenstemming met Good Clinical Practice (GCP) en de methoden werden vooraf gespecificeerd in een protocol. De behandelingsduur was 6 maanden, gevolgd door een medicatievrije follow-up periode van 6 maanden. Het primaire eindpunt was de cumulatieve abstinentieduur (CAD) gedurende de behandelperiode van 6 maanden. Secundaire eindpunten waren de CAD gedurende de gehele studieperiode van 12 maanden. CAD meet het aantal dagen zonder alcoholgebruik voor elke patiënt. De studie was positief in de vooraf gespecificeerde primaire analyse van het primaire eindpunt: SMO toonde een statistisch zeer significante en klinisch relevant hogere CAD na 6 maanden behandeling: gecorrigeerd gemiddeld verschil +43,1 dagen. De robuustheid van deze bevinding werd ondersteund door verschillende gevoeligheidsanalyses die allemaal een significant effect van SMO lieten zien met vergelijkbare puntschattingen. Bovendien bleef de werkzaamheid van SMO in CAD behouden tijdens de onbehandelde follow-up periode van 6 maanden (**hoofdstuk 3**). Het risico van bias voor de resultaten van de primaire uitkomst van deze studie werd laag geacht (**hoofdstuk 5**). Een beoordeling aan de hand van de GRADE-criteria

ondersteunt een hoge kwaliteit van bewijs voor de werkzaamheid van SMO in CAD in deze studie (**hoofdstuk 7**).

Belangrijk is dat het primaire eindpunt van de GATE 2 studie verschilt van het eindpunt dat momenteel door EMA wordt aanbevolen voor fase III-proeven, namelijk het continue abstinentiepercentage (het percentage patiënten dat gedurende de gehele behandelperiode continue abstinent is). CAD kan echter worden opgevat als een samengesteld eindpunt dat zowel het continue abstinentiepercentage als de abstinentieduur van patiënten die terugvallen meet. De werkzaamheid van SMO in CAD werd verklaard door een hoger continu abstinentiepercentage en een langere abstinentieduur bij patiënten die terugvielen in de SMO-groep vergeleken met de placebogroep (**hoofdstuk 3**). Daarom ondersteunen deze gegevens de bewering dat SMO (≈50mg/kg/dag) een statistisch significante en klinisch relevante werkzaamheid heeft in de GATE 2 studie met een hoge kwaliteit van bewijs.

De dosis-responsrelatie van SMO werd onderzocht in een fase IIb internationale, dubbelblinde, placebogecontroleerde RCT (SMO032 studie) bij 509 AA-patiënten, waarbij de werkzaamheid en veiligheid bij het handhaven van abstinentie werd getest van vier doses van een SMO-formulering die misbruik/doorverkoop afschrikt, dat wil zeggen met gebruikmaking van SMO-korrels in plaats van een SMO-oplossing (**hoofdstuk 2**). Verkennende analyses toonden een dosis-responsrelatie tussen SMO en alcoholuitkomsten die werd beïnvloed door het niveau van het alcoholgebruik bij aanvang van de studie en het lichaamsgewicht van de patiënt: hoe meer alcohol bij aanvang werd geconsumeerd, hoe hoger de SMO-dosis in mg/kg die moest worden toegediend voor een positief effect. Bij zwaar drinkende AA-patiënten had een dosis SMO van 60mg/kg/dag de beste respons (**hoofdstuk 2**). De gevonden dosis-respons relatie komt overeen met de farmacologie van SMO en de dosis-respons die in preklinische studies werd waargenomen. De rol van SMO als substituut voor alcohol wordt ondersteund door de werkzaamheid van SMO bij de behandeling van het AOS in verscheidene studies, meta-analyses en in klinische studies die vergelijkbare effecten lieten zien tussen ethanol en SMO. Aangezien deze dosis-respons bevindingen gebaseerd zijn op een verkennende analyse en er bij deze doses geen veiligheidsproblemen werden gemeld, zou de behandeling met SMO kunnen worden gestart met een dosis van 50mg/kg/dag en worden verhoogd tot 60mg/kg/dag in geval van onvoldoende behandelingsrespons bij AA-patiënten die zwaar drinken (**hoofdstuk 7**).

Zowel in de GATE 2- als de SMO032-studie was er sprake van een substantiële heterogeniteit van het SMO-behandeleffect. In de GATE 2 RCT (**hoofdstuk 3**) werd een significante en substantiële heterogeniteit van het behandeleffect op CAD tussen locaties vastgesteld. Het geschatte SMO-behandeleffect op CAD was groter op locaties met een lagere placeborespons. In de SMO032 RCT

(**hoofdstuk 2**) werd het aantonen van de werkzaamheid op het primaire eindpunt, namelijk het percentage abstinente dagen (PDA), waarschijnlijk bemoeilijkt door een onverwacht hoge placeborespons (gemiddeld 73%) die veel hoger was dan de placeborespons in de GATE 2-studie (gemiddeld 38%). In het algemeen suggereren deze gegevens een verband tussen het effect van de SMO-behandeling en de placeborespons in een bepaalde populatie. Daarom was het van belang het effect van de ernst van de populatie en de duur van de behandeling op zowel de placeborespons als het SMO-behandeleffect te onderzoeken.

In **hoofdstuk 4** werd met behulp van meta-regressieanalyse - op basis van 19 placebo-gecontroleerde RCT's en 1.996 AA-patiënten die met een placebo behandeld werden - het effect van de populatie-ernst en de behandelduur op de placeborespons onderzocht met het continue abstinentiepercentage als uitkomstmaat. De percentage continue abstinentie in de placebo-groepen hing significant samen met de ernst van de populatie en de behandelduur en was lager in de groep studies met een hoge ernstgraad dan in de groep studies met een milde ernstgraad en in studies met een langere versus een kortere geplande behandelingsduur. Daarom is de aantonen van een geneesmiddeleffect (indien werkelijk aanwezig) waarschijnlijker in de populatie met een hoge ernstgraad. Deze bevindingen kunnen de doeltreffendheid van de toekomstige geneesmiddelenontwikkeling voor AA verbeteren.

Vervolgens onderzochten we het modererende effect van de ernst van de populatie en de duur van de behandeling op de werkzaamheid van SMO bij het handhaven van abstinentie binnen de klinische studies. In de SMO032 RCT (**hoofdstuk 2**) toonde een subgroep analyse een significante en klinisch relevante werkzaamheid van SMO in de populatie met een hoge ernstgraad in zowel het percentage continue abstinentie als PDA, waarschijnlijk als gevolg van een lagere placeborespons in deze ernstige subgroep. Het SMO-behandeleffect nam toe, en de placeborespons nam af met een langere behandelingsduur. SMO gaf geen verbetering in de groep met lichte ernst, waarschijnlijk als gevolg van een zeer hoge placeborespons, waardoor er voor het actieve medicijn (SMO) bijna geen ruimte voor verbetering overbleef. De andere placebogecontroleerde RCT's waarin de werkzaamheid van SMO werd getest, werden uitsluitend uitgevoerd bij een populatie met een hoge ernst of een populatie met een milde ernst, waardoor de analyse binnen de studie van het effect op de ernst van de populatie op de uitkomst niet kon worden onderzocht.

In **hoofdstuk 5 werd** het effect van de ernst van de populatie en de duur van de behandeling op de werkzaamheid van SMO in verschillende proeven getest met behulp van een netwerk meta-regressieanalyse van acht studies met in totaal 1.082 behandelde AA-patiënten. De groep studies met een hoge ernst was geassocieerd met significant grotere SMO-effectgroottes dan de groep studies met een milde ernst, zowel voor continu abstinentiepercentage als voor PDA.

Voor PDA was een langere behandelduur ook geassocieerd met een grotere SMO-effectgrootte. Gezien deze interactie-effecten werd de werkzaamheid van SMO vervolgens in elke populatie-ernstgroep afzonderlijk onderzocht met behulp van een netwerk-meta-analyse. In de ernstige groep had SMO een significant effect voor zowel het continue abstinentiepercentage als voor PDA, met grote effectgroottes. In de milde groep toonde SMO alleen een significant effect in PDA en alleen bij een langere behandelduur.

Deze meta-regressies en subgroep analyses geven een (gedeeltelijke) verklaring op voor de heterogeniteit van de werkzaamheid van SMO. Aanwezigheid van (rest)bias en/of vertekening kan echter niet worden uitgesloten in meta-regressieanalyses. Daarom is er op basis van EMA- en Cochrane-criteria gekeken naar de betrouwbaarheid en plausibiliteit van de door ons uitgevoerde verkennende subgroep analyses en meta-regressies. Op basis van deze bevindingen menen wij dat er waarschijnlijk een causaal verband bestaat tussen de ernst van de populatie en de duur van de behandeling en het SMO-behandelingseffect. Deze kennis kan zorgverleners helpen bij het gebruik van SMO voor een (gepersonaliseerde) behandeling van AA-patienten (**hoofdstuk 5**).

Uit bovenstaande blijkt SMO (het meest) effectief te zijn bij de groep patiënten met een hoge ernstgraad, waaronder AA-patiënten met een zeer hoog alcoholgebruik. In **hoofdstuk 6** schatten wij dat, hoewel zij minder dan 1% van de algemene bevolking tussen 15 en 64 jaar uitmaken, zeer zware drinkers verantwoordelijk zijn voor een aanzienlijk deel van de aan alcohol toe te schrijven ziekten en een levensverwachting hebben van slechts 47-61 jaar. In **hoofdstuk 4** wordt gesuggereerd dat meer dan twee derde van de patiënten in de populatie van zeer zware drinkers er niet in slaagt abstinentie te handhaven met de bestaande interventies (afgezien van SMO), hetgeen wijst op een belangrijke behoefte aan aanvullende effectieve interventies bij deze patiëntenpopulatie.

In de studies GATE 2 en SMO032 werd SMO goed verdragen. De meest gemelde bijwerkingen (AE's) waren hoofdpijn en duizeligheid. In deze studies werden geen fatale ernstige bijwerkingen gemeld die verband hielden met de studiemedicatie, en de incidentie van niet-fatale ernstige bijwerkingen (SAEs) was vergelijkbaar voor de SMO- en placebogroepen. De hunkering naar medicatie (‘craving’) was vergelijkbaar in de SMO- en placebogroepen in beide studies. In beide studies werden geen gevallen van misbruik gemeld. Er werden ook geen gevallen van misbruik of overdosering gemeld met de nieuwe formulering van SMO-korrels ter afschrikking van misbruik/doorverkoop. Bij één patiënt (0,6%) was sprake van een overdosis SMO-oplossing, wat mogelijk wijst op een beter veiligheidsprofiel van SMO-korrels (**hoofdstukken 2 en 3**).

In **hoofdstuk 7 worden** toekomstige richtingen van onderzoek en toepassing besproken, met name onderzoek naar het effect van de ernst van de populatie en

de duur van de behandeling op de werkzaamheid van andere farmacologische behandelingen, een kosteneffectiviteitsanalyse van SMO bij de behandeling van AA, en verdere studies naar de werkzaamheid en veiligheid van SMO bij AA-patiënten met leverfunctiestoornissen.

Dit proefschrift biedt ook gegevens om tegemoet te komen aan de zorgen die EMA heeft geuit tijdens diverse evaluaties van de klinische studies met SMO van 2017 tot 2020 die eindigden in een negatief besluit over goedkeuring van het gebruik van SMO in de EU. Het in dit proefschrift gepresenteerde werk biedt een klinisch wetenschappelijk pakket dat de werkzaamheid en de gunstige voordeel-risico balans van SMO bij het handhaven van abstinentie bij AA-patiënten ondersteunt en mogelijk kan worden gebruikt in toekomstige registratieprocedures (**hoofdstuk 7**).

PhD portfolio

Name PhD student: Guiraud Julien		
PhD period: January 2019 – May 2023		
Names of PhD supervisors & co-supervisor:		
Prof. Dr. W. van den Brink, Prof. Dr. A.E. Goudriaan, Prof. Dr. R. Spanagel.		
1. PhD training		
	Year	**Hours**
Specific courses		
- Trials methodology, quality of evidence rating, benefit risk assessment	2019-2022	50
Self-study courses		
- EMA guidelines on efficacy, safety, pharmacovigilance	2019-2022	100
- FDA guidelines on efficacy and safety	2019-2022	20
- ICH guidelines on efficacy and safety, including GCP	2019-2022	50
- GRADE guidelines	2019-2022	20
- Cochrane Handbook	2019-2022	40
- Cochrane risk of bias assessment	2020-2022	30
- Statistics: linear & meta regressions, meta-analyses, multiple imputation	2020-2022	60
- STATA programming e-courses	2020-2022	20

Presentations		
- Presentation/discussion of sodium oxybate proposed risk minimization measures to 18 EU regulatory authorities – June to September 2019	2019	200
- Presentation/discussion of sodium oxybate data to the CHMP – September 2019	2019	40
- Presentation/discussion of sodium oxybate data to the ad-hoc expert group convened by EMA – February 2020	2020	40
- Presentation/discussion of sodium oxybate data to the ad-hoc expert group convened by EMA – April 2020	2020	20
- Presentation/discussion of sodium oxybate data to the CHMP – April 2020p	2020	40
(Inter)national conferences		
- SFA, March 2019, Amiens, France (participant)	2019	10
- Albatros, December 2021, Paris, France (participant)	2021	20
- Albatros, June 2022, Paris, France (presentation of a meta-regression analysis of sodium oxybate studies)	2022	40

Other – experience/knowledge gained during registration procedure of sodium oxybate for the treatment of alcohol dependence		
- Medical writing: clinical study report for phase III study, eCTD modules with Clinical Overviews, Clinical Summaries, Risk Management Plans	2019-2023	700
- Preparation of written responses to 100+ questions raised by the European Medicines Agency on sodium oxybate data limitations	2019-2020	700
- Check of statistical computations made by the clinical research organizations	2020-2022	50

2. Teaching		
	Year	**Hours**
Other		
- Management and supervision of 10+ R&D employees	2019-2021	900

3. Parameters of Esteem	
	Year
Grants - Not applicable as no application	
Awards and Prizes - None	

4. Publications	
	Year
Peer reviewed	
- Rehm J, Guiraud J, Poulnais R, Shield KD. Alcohol dependence and very high risk level of alcohol consumption: a life-threatening and debilitating disease. Addict Biol. 2018 Jul;23(4):961-968. doi: 10.1111/adb.12646. PMID: 30043407	2018
- Scherrer B, Guiraud J, Addolorato G, Aubin HJ, de Bejczy A, Benyamina A, van den Brink W, Caputo F, Dematteis M, Goudriaan AE, Gual A, Kiefer F, Leggio L, Lesch OM, Maremmani I, Nutt DJ, Paille F, Perney P, Poulnais R, Raffaillac Q, Rehm J, Rolland B, Simon N, Söderpalm B, Sommer WH, Walter H, Spanagel R. Baseline severity and the prediction of placebo response in clinical trials for alcohol dependence: A meta-regression analysis to develop an enrichment strategy. Alcohol Clin Exp Res. 2021 Sep;45(9):1722-1734. doi: 10.1111/acer.14670. Epub 2021 Aug 21. PMID: 34418121; PMCID: PMC9291112.	2021
- Guiraud J, Addolorato G, Aubin HJ, Batel P, de Bejczy A, Caputo F, Goudriaan AE, Gual A, Lesch O, Maremmani I, Perney P, Poulnais R, Raffaillac Q, Soderpalm B, Spanagel R, Walter H, van den Brink W; SMO032 study group. Treating alcohol dependence with an abuse and misuse deterrent formulation of sodium oxybate: Results of a randomised, double-blind, placebo-controlled study. Eur Neuropsychopharmacol. 2021 Nov;52:18-30. doi: 10.1016/j.euroneuro.2021.06.003. Epub 2021 Jul 6. PMID: 34237655.	2021
- Guiraud J, Addolorato G, Antonelli M, Aubin HJ, de Bejczy A, Benyamina A, Cacciaglia R, Caputo F, Dematteis M, Ferrulli A, Goudriaan AE, Gual A, Lesch OM, Maremmani I, Mirijello A, Nutt DJ, Paille F, Perney P, Poulnais R, Raffaillac Q, Rehm J, Rolland B, Rotondo C, Scherrer B, Simon N, Skala K, Söderpalm B,	2022

4. Publications	
	Year
Somaini L, Sommer WH, Spanagel R, Vassallo GA, Walter H, van den Brink W. Sodium oxybate for the maintenance of abstinence in alcohol-dependent patients: An international, multicenter, randomized, double-blind, placebo-controlled trial. J Psychopharmacol. 2022 Oct;36(10):1136-1145. doi: 10.1177/02698811221104063. Epub 2022 Jul 7. PMID: 35796481; PMCID: PMC9548946.	
- Guiraud J, Addolorato G, Aubin HJ, Bachelot S, Batel P, de Bejczy A, Benyamina A, Caputo F, Couderc M, Dematteis M, Goudriaan AE, Gual A, Lecoustey S, Lesch OM, Maremmani I, Nutt DJ, Paille F, Perney P, Rehm J, Rolland B, Scherrer B, Simon N, Söderpalm B, Somaini L, Sommer WH, Spanagel R, Walter H, van den Brink W. Sodium Oxybate for Alcohol Dependence: A Network Meta-Regression Analysis Considering Population Severity at Baseline and Treatment Duration. Alcohol Alcohol. 2023 Jan 6:agac070. doi: 10.1093/alcalc/agac070. Epub ahead of print. PMID: 36617267.	2023
Other	
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List of publications

PUBLICATIONS

Published

Guiraud, J., Addolorato, G., Antonelli, M., Aubin, H.-J., de Bejczy, A., Benyamina, A., Cacciaglia, R., Caputo, F., Dematteis, M., Ferrulli, A., Goudriaan, A.E., Gual, A., Lesch, O.-M., Maremmani, I., Mirijello, A., Nutt, D.J., Paille, F., Perney, P., Poulnais, R., Raffaillac, Q., Rehm, J., Rolland, B., Rotondo, C., Scherrer, B., Simon, N., Skala, K., Söderpalm, B., Somaini, L., Sommer, W.H., Spanagel, R., Vassallo, G.A., Walter, H., van den Brink, W., 2022. Sodium oxybate for the maintenance of abstinence in alcohol-dependent patients: An international, multicenter, randomized, double-blind, placebo-controlled trial. J Psychopharmacol 026988112211040. https://doi.org/10.1177/02698811221104063

Guiraud, J., Addolorato, G., Aubin, H.-J., Bachelot, S., Batel, P., de Bejczy, A., Benyamina, A., Caputo, F., Couderc, M., Dematteis, M., Goudriaan, A.E., Gual, A., Lecoustey, S., Lesch, O.-M., Maremmani, I., Nutt, D.J., Paille, F., Perney, P., Rehm, J., Rolland, B., Scherrer, B., Simon, N., Söderpalm, B., Somaini, L., Sommer, W.H., Spanagel, R., Walter, H., van den Brink, W., 2023. Sodium Oxybate for Alcohol Dependence: A Network Meta-Regression Analysis Considering Population Severity at Baseline and Treatment Duration. Alcohol and Alcoholism agac070. https://doi.org/10.1093/alcalc/agac070

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Rehm, J., **Guiraud, J.**, Poulnais, R., Shield, K.D., 2018. Alcohol dependence and very high risk level of alcohol consumption: a life-threatening and debilitating disease. Addiction Biology 23, 961–968. https://doi.org/10.1111/adb.12646

Scherrer, B.*, **Guiraud, J.***, Addolorato, G., Aubin, H., Bejczy, A., Benyamina, A., Brink, W., Caputo, F., Dematteis, M., Goudriaan, A.E., Gual, A., Kiefer, F., Leggio, L., Lesch, O., Maremmani, I., Nutt, D.J., Paille, F., Perney, P., Poulnais, R., Raffaillac, Q., Rehm, J., Rolland, B., Simon, N., Söderpalm, B., Sommer, W.H., Walter, H., Spanagel, R., 2021. Baseline severity and the prediction of placebo response in clinical trials for alcohol dependence: A meta-regression analysis to develop an enrichment strategy. Alcohol Clin Exp Res acer.14670. https://doi.org/10.1111/acer.14670. * contributed equally.

Author’s contributions

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Bachelot, S.	SB	Lesch, O.-M.	OML	Skala, K.	KS
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Dematteis, M.	MD	Raffaillac, Q.	QR	van den Brink, W.	WvdB
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Goudriaan, A.E.	AEG	Rolland, B.	BR		

In addition to the above authors, clinical research organizations (CROs) were involved in the phase IIb (Chapter 2) and in the phase III (Chapter 3) studies.

CHAPTER 2

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

Guiraud, J., Addolorato, G., Aubin, H.-J., Batel, P., de Bejczy, A., Caputo, F., Goudriaan, A.E., Gual, A., Lesch, O., Maremmani, I., Perney, P., Poulnais, R., Raffaillac, Q., Soderpalm, B., Spanagel, R., Walter, H., van den Brink, W.

Conception and design	OML and JG
Data collection	CRO
Statistical analyses	CRO, JG, QR, RP, and BS
Data-analysis/interpretation	All authors
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Responses to reviewer comments/manuscript revision	JG and WvdB
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CHAPTER 3

Sodium oxybate for the maintenance of abstinence in alcohol-dependent patients: An international, multicenter, randomized, double-blind, placebo-controlled trial.

Guiraud, J., Addolorato, G., Antonelli, M., Aubin, H.-J., de Bejczy, A., Benyamina, A., Cacciaglia, R., Caputo, F., Dematteis, M., Ferrulli, A., Goudriaan, A.E., Gual, A., Lesch, O.-M., Maremmani, I., Mirijello, A., Nutt, D.J., Paille, F., Perney, P., Poulnais, R., Raffaillac, Q., Rehm, J., Rolland, B., Rotondo, C., Scherrer, B., Simon, N., Skala, K., Söderpalm, B., Somaini, L., Sommer, W.H., Spanagel, R., Vassallo, G.A., Walter, H., van den Brink, W.

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Statistical analyses	CRO, JG, QR, RP, and BS
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CHAPTER 4

Baseline severity and the prediction of placebo response in clinical trials for alcohol dependence: A meta-regression analysis to develop an enrichment strategy.

Scherrer, B., Guiraud, J.*, Addolorato, G., Aubin, H., Bejczy, A., Benyamina, A., Brink, W., Caputo, F., Dematteis, M., Goudriaan, A.E., Gual, A., Kiefer, F., Leggio, L., Lesch, O., Maremmani, I., Nutt, D.J., Paille, F., Perney, P., Poulnais, R., Raffaillac, Q., Rehm, J., Rolland, B., Simon, N., Söderpalm, B., Sommer, W.H., Walter, H., Spanagel, R. * contributed equally.*

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Responses to reviewer comments/manuscript revision	JG, BS, RS and WvdB
Critical review of the responses/revisions	All authors
Supervision	RS, WvdB, and AEG
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CHAPTER 5

A Network Meta-Regression Analysis Considering Population Severity at Baseline and Treatment Duration.

Guiraud, J., Addolorato, G., Aubin, H.-J., Bachelot, S., Batel, P., de Bejczy, A., Benyamina, A., Caputo, F., Couderc, M., Dematteis, M., Goudriaan, A.E., Gual, A., Lecoustey, S., Lesch, O.-M., Maremmani, I., Nutt, D.J., Paille, F., Perney, P., Rehm, J., Rolland, B., Scherrer, B., Simon, N., Söderpalm, B., Somaini, L., Sommer, W.H., Spanagel, R., Walter, H., van den Brink, W.

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Responses to reviewer comments/manuscript revision	JG and WvdB
Critical review of the responses/revisions	All authors
Supervision	WvdB, RS, and AEG
Support to get funding	JG, RS

CHAPTER 6

Alcohol dependence and very high risk level of alcohol consumption: a life-threatening and debilitating disease.

Rehm, J., Guiraud, J., Poulnais, R., Shield, K.D.

Conception and design	JG, JR, and RP
Data collection	JG and RP
Statistical analyses	JG and RP
Data-analysis/interpretation	All authors
Drafting of the manuscript	JR and KDS
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Responses to reviewer comments/manuscript revision	JR and KDS
Critical review of the responses/revisions	JG and RP
Supervision	JR and KDS
Support to get funding	JG, JR

About the author

Julien Guiraud was born on December 8, 1978 in Marseille (France). He obtained a Master of Science in aeronautical engineering of ISAE-Supaero, Toulouse, France, in 2002. He then received a Specialized Master degree in audit (summa cum laude) of HEC Paris, France, in 2003.

He worked at KPMG Audit Paris from 2002 to 2010, occupying positions from auditor (2002) to senior manager (2010). He was responsible for an important part of the financial audit of the Airbus group and managed international teams located in four EU countries. He was involved in various strategic issues and worked on the A380, A400M, and A350 programs with direct reporting to Airbus group top management, including the Chief Financial Officer (CFO).

He joined D&A Pharma in 2010 as CFO and was promoted Chief Executive Officer (CEO) in 2014. As CFO, he managed the Group's finance, the financial planning and risks, and the restructuring of a subsidiary and was responsible for/involved in the sale of assets and fundraisings to finance the clinical development of Alcover/Hopveus (sodium oxybate for the treatment of alcohol dependence). As CEO, he managed the completion of the development and the registration procedures of Alcover/Hopveus in the EU (decentralized and centralized procedures) from 2014 to 2022. He was involved in clinical development including Phase II and III trials, statistical analyses, preparation of clinical modules and risk management plan of marketing authorization application dossiers (eCTD), centralized and decentralized registration procedures, orphan drug designation, conditional marketing authorization application as well as generic and full applications. He was the Company's main speaker in meetings at the European Medicines Agency (scientific advisory group meetings, oral explanations at CHMP, pre-submission meetings) and at various national medicines agencies in the EU. He worked closely with a group of 20+ international researchers in the alcohol addiction field and with former assessors from medicines agencies, senior methodologists, and statisticians. He oversaw a team of 40+ employees in 3 locations.

In 2022, after 8 years as CEO of D&A Pharma, he decided to found Vergio, a company that aims to provide holistic solutions for drug development.

In 2020, to value the acquired skills and expand them, he decided to apply for a doctoral programme at the University of Amsterdam.

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This research work and pharmaceutical development as well as the steps prior to this doctoral program have been for me a unique, both incredibly rich and difficult journey.

Unique because I think it is quite unusual to be involved in Phase II & III clinical trials, conduct research work, manage registration procedures, and eventually carry out a doctoral program on sodium oxybate for the treatment of alcohol dependence with an aeronautical engineer degree, a 12-year initial experience in finance, and 10+ years as corporate executive.

Difficult, not for the doctoral program by itself which has been really fun but for all hardships that occurred before the initiation of this program and that were essentially linked with the registration procedures of sodium oxybate. They were however extremely formative and somehow allowed me to do this doctoral program.

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Supplementary materials are available online:

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