There is a need for a noninvasive and more acceptable method to the patients, to assess alcohol abuse/dependence. Therefore, the attention of researchers to the saliva in recent years increased. The obtaining of salvia is easy, it does not carry the risk of needle-stick injuries, it less likely causes stress, and there is no need for trained staff because self-collection after instruction is possible. In addition, saliva contains a wide array of constituents that are very sensitive to toxic substances, and lastly, saliva samples can reflect real-time levels of biomarkers as compared to the urine that is non-invasively collected but stored in the bladder for a few hours before sampling. Ethanol diffuses rapidly into saliva and oral tissues, and its concentration is temporarily higher than in plasma; whereas the level of ethanol metabolite-acetaldehyde in saliva exceeds 10-100 times the blood level. Besides acetaldehyde and reactive oxygen species (ROS) generated during drinking, non-oxidative metabolites of ethanol (e.g., fatty acid ethyl esters) and the ethanol-water-competition mechanism, might also be involved in the resulting damage of the oral tissue and formation of a new salivary alcohol biomarkers. Saliva has earlier been proposed for the detection of alcohol abuse by the determination of salivary ethanol, aminotransferases and gammaglutamyl-transferase, ethanol, methanol, diethylene/ethylene glycol, or sialic acid. The alcohol-induced immunological and metabolic errors may also result in the formation of a novel biomarkers of alcohol abuse such as β-hexosaminidase A (HEX A) or HEX A \% (β-HEX A to total β-HEX), oral peroxidase, immunoglobulin A.

**SAT1.3**

**CLINICAL DATA SUPPORTING THE BENEFIT OF A PATIENT-CENTRED APPROACH IN THE TREATMENT OF ALCOHOL DEPENDENCE**

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A patient centred approach that offers the choice of reduction of alcohol consumption as part of a continuum of treatment goals and which allows patients to have a say in dosing regimens, may help reduce the barriers to treatment perceived by some individuals. Engaging patients in managing their treatment may also improve adherence. In three phase III studies assessing as-needed nalmefene in reducing alcohol consumption in alcohol dependent patients, it has been shown that alcohol dependent patients understand, accept and adhere to the “as-needed” dosing concept and that nalmefene as-needed reduces the average daily total alcohol consumption (TAC; g/day) and number of heavy drinking days (HDDs). The W.H.O. has defined risk categories for health problems based on the level of daily alcohol consumption. These categories can be used to define response, as a measure of the clinical relevance of the reduction in alcohol consumption at an individual patient level. Drinking variables (TAC and HDDs) were measured using Timeline Follow-Back. Various analyses were used to translate the reduction in alcohol consumption into clinically relevant responses. Response was defined as 1) two-category down-shift in drinking risk level; 2) downward shift to low drinking risk level; 3) 70% reduction in TAC; all at month 6. As-needed nalmefene was associated with each of these clinically relevant responses, supporting that the benefits of a patient-centered approach can be shown in clinical trials.

**SAT2**

**SODIUM OXYBATE, A BREAKTHROUGH TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME AND MAINTENANCE OF ALCOHOL ABSTINENCE (D&A)**

**SAT2.1**

**SODIUM OXYBATE IN ALCOHOL WITHDRAWAL – RESULTS FROM THE GATE 1 STUDY**

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**Background.** Alcohol withdrawal can be a difficult challenge as most substances available are of limited efficacy according to withdrawal and relapse prevention in early stages. We aimed to investigate safety and efficacy of sodium 4-hydroxybutyrate (sodium oxybate or GHB) in the withdrawal treatment of alcohol dependent patients.

**Method.** 126 patients with a diagnosis of alcohol dependence according to DSM-IV criteria with severe withdrawal (CIWA-Ar Scale: 18.71 vs. 18.00) were randomly recruited from 9 European sites and allocated to treatment with sodium oxybate (n = 61) or oxazepam (n = 65) in a double blind, double dummy design. Daily dosage in the first 5 days was 5.25 g (i.e.30 ml) for sodium oxybate and 210 mg for oxazepam, adjusted for body weight. The medication dropped down until day 10. Primary outcome variable was severity of withdrawal as determined with CIWA-Ar scale.

**Findings.** Patients were comparable in demographic details and there was no difference in the distribution of Lesch’s types or the severity of withdrawal symptoms between groups (also in biological markers and craving for alcohol). In both groups withdrawal and craving for alcohol decreased significantly, with no difference between the treatment groups. In both groups nearly alcohol consumption and number of heavy drinking days and to improve liver functions and clinical status in two 6-month studies (identically designed), and one 1-year study in patients with alcohol dependence. The benefit of nalmefene was further studied in the pooled subgroup of patients from the 6-month studies. The patients in this subgroup were consuming alcohol at a high drinking risk level at the initial assessment (screening) and at the start of treatment (baseline). In this subgroup, identified as most likely to benefit, the net treatment effect over placebo in terms of reduction of alcohol consumption was more pronounced.
all patients stayed sober the whole treatment and follow up period (90.2% vs. 84.6%). The biological markers normalized in both groups significantly without any group differences. Neither cognitive impairment nor adverse events were found more often in one of the groups.

**Interpretation.** Sodium oxybate and oxazepam are both effective and safe in treating alcohol withdrawal and in reducing craving for alcohol. Any kind of craving after discontinuation of sodium oxybate or of oxazepam was not an issue. Motivation process could be started early in both groups.

**SAT2.2**

**SODIUM OXYBATE IN THE PREVENTION OF ALCOHOL RELAPSES IN ALCOHOL DEPENDENT PATIENTS (GATE 2 STUDY)**

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**Background.** Maintenance of abstinence from alcohol represents the most important, but also the most challenging objective in the treatment of alcohol dependent patients. We aimed to investigate the long-term safety and efficacy of sodium oxybate in the long-term treatment of recently detoxified alcohol-dependent patients.

**Method.** 314 patients with a diagnosis of alcohol dependence according to DSM-IV criteria were randomly enrolled from 11 European sites and allocated to two treatment groups: sodium oxybate (n = 154) and placebo (n = 160). Study duration was of 12 months (6 months of double-blind treatment period and 6 months of untreated follow-up). The primary outcome was the Cumulative Abstinence Duration (CAD).

**Findings.** Sodium oxybate was superior to placebo in achieving and maintaining abstinence from alcohol (p = 0.05). Specifically, sodium oxybate was particularly effective in Lesch type II patients (p = 0.035), but also in Lesch type III and IV patients (not statistically significant because of a lower sample size). Moreover, the incidence of craving for and abuse of the drug, and of other safety endpoints did not differ between sodium oxybate and placebo groups.

**Interpretation.** This long-term study confirms the safety and efficacy of sodium oxybate in promoting and maintaining abstinence from alcohol in recently detoxified alcoholics, particularly, but not only, in Lesch type II alcohol-dependent patients. In addition, we found no evidence of abuse, misuse or dependence for the drug in this large patient population.

Funding: Laboratorio Farmaceutico CT S.r.l.

**SAT2.3**

**PHARMACODYNAMIC INTERACTIONS OF A SOLID FORMULATION OF SODIUM OXYBATE AND ALCOHOL IN HEALTHY VOLUNTEERS:**

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**Background.** Sodium oxybate shares some pharmacological effects with alcohol, and has been approved for the treatment of alcohol dependence in Europe. This study evaluated the pharmacodynamic interactions of SMO.IR, a solid formulation of sodium oxybate and alcohol, to assess possible synergism, potentiation or antagonism of SMO.IR and alcohol.

**Methods.** 24 healthy volunteers participated in a double-blind crossover trial. Study participants randomly received: SMO.IR alone, alcohol alone, SMO.IR + alcohol, and double placebo. Study endpoints were objective and subjective cognitive tests, adverse events, vital signs assessed before, and 15 and 165 minutes post dose. Cognitive tests included: Body Sway Test, Saccadic Eye Movement, Choice Reaction Time, Critical Tracking Test, Digit Vigilance, Numerical and, Spatial Working Memory, Bond & Lader VAS, ARC1 49, and Biphasic Alcohol Effects Scale.

**Results.** Alcohol produced a significant impairment in cognitive performance and subjective sedation at 15 min. SMO.IR-induced less pronounced objective and subjective sedation 165 min post dose. There was a significant interaction between SMO.IR and alcohol, at 15 min, with an increase in alertness and stimulation and a decrease in sedation. An isolated mild decrease in digit vigilance accuracy was observed at 165 minutes post dose with the combination. The combination increased the number of treatment-emergent adverse events: 46 vs 30 with SMO.IR and 34 with alcohol. No significant changes in vital signs, oxygen saturation, and laboratory tests were observed.

**Conclusion.** SMO.IR and alcohol have a distinct pharmacodynamic profile. Sedative effects of SMO.IR are much less marked than those of alcohol and no reciprocal potentiation was observed.

**SAT2.4**

**A RETROSPECTIVE STUDY ON THE USE OF SODIUM OXYBATE IN northern ITALY**

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**Background.** The Sodium Oxybate is successfully used in Italy from over fifteen years for the treatment of both alcohol withdrawal and relapse prevention. The principal aim of this retrospective study, named GUM (GHB use and misuse), was to evaluate the effectiveness and the safety of Sodium Oxybate in the daily clinical practice.

**Method.** The study analysed 485 individuals (604 treatment cycles), with a diagnosis of alcohol dependence according to DSM-IV criteria, treated with Sodium Oxybate at seven alcoholism rehabilitation centers in northern Italy in the years 2005–2007. The primary outcomes of the study were: the drug anti-withdrawal effects; the drug effects on relapse prevention, the treatment drop out rate; while the secondary outcomes were: the drug side effects and adverse reactions, the appeitite behaviour ("misuse"), the drug abuse and the overdose, intoxication and withdrawal episodes. Finally, the study evaluated, for the first time, in a large cohort of Italian alcoholics, the prevalence of both infection diseases (e.g. hepatitis C, HIV, etc.) and prevalent psychiatric illness (including personality disorders).

**Findings.** The study confirmed the effectiveness of Sodium Oxybate in suppressing withdrawal syndrome (81% of the subjects treated were successfully rehabilitated) and in maintaining abstinence (76% and 78% of patients were abstinent at six and twelve months after starting treatment). The study showed that the drug is also safe and manageable, especially if used in doses between 50 and 100 mg/die (the average dose was between 78.11 + 22.30 mg/kg/die). Misuse and abuse were limited (12% of treatments), cases of intoxication an overdose extremely rare. For the first time in Italy, the study helped to identify the main demographics and clinical features of a significant sample of alcoholics subjects treated with Sodium Oxybate and the prevalence of prevalent infections diseases (31 % were HBeAb + HBsAg positive, 15% were HCV positive and 4 % were HIV positive) and psychiatric illnesses (12% in Axis I and 4% in Axis II).

**Interpretation.** The GUM study confirms the effectiveness and the safety of Sodium Oxybate in the treatment of subjects undergoing rehabilitation in Italian alcohol treatment centers. Funding: Laboratorio Farmaceutico CT S.r.l.

**FREE ORAL COMMUNICATIONS**

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**FREE ORAL COMMUNICATIONS 1: BASIC NEUROBIOLOGICAL MECHANISMS OF ALCOHOL ADDICTION**

O1.1

**DYNAMIC REGULATION OF MIR-9 PATHWAYS BY ALCOHOL**

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microRNAs are master regulators of gene expression. They are particularly important in brain function. Previously, we observed that short exposure to 20mM ethanol upregulated mir-9 in primary rodent neuronal cultures or brain organotypic slices. These observations prompted us to perform more detailed temporal characteristics and dose-dependence of mir-9 response to ethanol using a regimen of ethanol exposures and withdrawals. We used two physiologically-relevant ethanol concentrations 20 mM and 50 mM. Exposure and/or withdrawal ranged from 15 minutes to 24 hours. We used postnatal day 5 striatal medium spiny neurons harvested from C57BL/6 mice. Total RNA