Supplementary Table 1. Characteristics of the 43 clinical studies included in the analysis

| **Study** | **Label** | **Study conducted in special population** | **Study design** | **Number of patients enrolled in the study** | **Number of patients exposed to SMO** | **Duration of the exposition to SMO** | **Dose** | **Number of adverse events reported** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Abanades et al., 2006 | L/M/H DRL | No | Double-blind, randomized, crossover, controlled | 8 | 8 | 4 x 1 day | 40; 50; 60; 72 mg/kg unique dose | 1 (Vomiting) |
| Addolorato et al., 1996 | Unknown DRL | No | Open, multicentric | 179 | 179 | 6 months | 50 mg/kg/day t.i.d. | 64 (Vertigo) |
| Addolorato et al., 1998 | Unknown DRL | No | Open | 154 | 154 | 16 weeks | 50 mg/kg/day in three or six intakes | None |
| Addolorato et al., 1999a | VH DRL | No | Randomized, Controlled | 60 | 30 | 10 days | 50 mg/kg/day t.i.d. | 5 ( Drowsiness/Vertigo) |
| Addolorato et al., 1999b | VH DRL | No | Longitudinal | 45 | 13 | 6 months | 50 mg/kg/day t.i.d. | None |
| Addolorato et al., 1999c | Unknown | No | Case report | 1 | 0 | 6 days | 20 mg diazepam | None |
| Avanzi et al., 1996 | Unknown DRL | No | Longitudinal | 44 | 44 | NR | NR | None |
| Barker et al., 2017 | HV | Yes (breastfeeding women) | Case report | 2 | 2 | NA | 6 to 9g per night | None |
| Borgen et al., 2003 – Food study | HV | No | Randomized, open-label | 36 | 36 | 1 day | 4.5g unique dose | 86 (Not specified) |
| Borgen et al., 2003 - Gender study | HV | No | Randomized, open-label | 36 | 36 | 1 day | 4.5g unique dose | 10 (Not specified) |
| Caputo et al., 2003 | Unknown DRL | No | Open, randomized | 35 | 18 | 3 months | 50 mg/kg/day t.i.d. | 1 (Vertigo) |
| Caputo et al., 2007 | Unknown DRL | No | Open, randomized | 20 | 20 | 3 months | 50 mg/kg/day t.i.d. | 2 (Vertigo) |
| Caputo et al., 2009 | VH DRL | No | Open | 47 | 14 | 3 months | 50 mg/kg/day t.i.d. | None |
| Caputo et al., 2009 | VH DRL  + polydrugs addiction | Yes (polydrug users) | Open | 47 | 33 | 3 months | 50 mg/kg/day t.i.d. | 2 (Vertigo) |
| Caputo et al., 2011 | VH DRL | No | Open | 48 | 20 | 12 weeks | 50 mg/kg/day t.i.d. | None |
| Caputo et al., 2011 | VH DRL + psychiatric comorbidities | Yes (patients with psychiatric comorbidities) | Open | 48 | 28 | 12 weeks | 50 mg/kg/day t.i.d. | 1 (Vertigo) |
| Caputo et al., 2014 | VH DRL | No | Open | 48 | 20 | 12 weeks | 50 mg/kg/day t.i.d. | 1 (Vertigo) |
| Caputo et al., 2014 | VH DRL + psychiatric comorbidities | Yes (patients with psychiatric comorbidities) | Open | 48 | 28 | 12 weeks | 50 mg/kg/day t.i.d. |
| Ceccanti et al., 1995 | VH DRL | No | Randomized | 42 | NR | 10 days | NR | None |
| Ceccanti et al., 1996 | Unknown | No | NR | 42 | NR | 10 days | 50 mg/kg/day t.i.d | None |
| Cibin & Zavan, 1995 | Unknown DRL | No | NR | 105 | 50 | 3.7 months | 41 mL/day (~720 mg/day | 3 (Dizziness, Cephelea, Mialgia) |
| Di bello et al., 1995 DB | VH DRL | No | Double-blind, randomized | 17 | 9 | 6 months | 50 mg/kg/day t.i.d | 2 (Diziness) |
| Di bello et al., 1995 Open 1 | VH DRL | No | Open | 14 | 14 | 6 days | 50-150 mg/kg/day t.i.d. | 2 (Diarrhoea) |
| Di bello et al., 1995 Open 2 | VH DRL | No | Open | 151 | 151 | 5 days | 50-100 mg/kg/day t.i.d. | 20 (Not specified) |
| Elsing et al., 2009 | Unknown DRL | No | Open, Randomized | 26 | 14 | 1 day | 30 mg/kg iv + 15 mg/kg iv | 2 (Deep sedation + unconsciousness, Respiratory distress) |
| Ferrara et al., 1992 | HV | No | PK | 10 | 10 | 7 days | 50 mg/kg/day b.i.d | 4 (Drowsiness) |
| Ferrara et al., 1996 | Unknown DRL | Yes (patients with hepatic impairment) | PK | 16 | 16 | 1 day | 25 mg/kg/day unique dose | 8 (Drowsiness + Diziness + Nausea) |
| Gallimberti et al., 1989 | Unknown DRL | No | Double-blind, randomized | 23 | 11 | 3 days | 50 mg/kg/day t.i.d | 7 (Dizziness) |
| Gallimberti et al., 1992 | VH DRL | No | Double-blind, randomized | 82 | 41 | 3 months | 50 mg/kg/day t.i.d | 6 (4 Vertigo+Dizziness, 2 Headache) |
| Gallimberti et al., 2000 | Unknown DRL | No | Retrospective | 195 | 138\*\* | NA | Up to 300 mg/kg/day | 215 (113 Vertigo, 41 Vomiting, 24 Diarrhoea 23 Nausea, 10 Bradypnea, 2 Psychotic reaction, 2 Convulsive reaction) |
| Gashlin et al., 2016 | HV | Yes (breasfeeding woman) | Case report | 1 | 1 | 6 months | 8 g per night | None |
| Korninger et al., 2003 | Unknown DRL | No | Open | 299 | 299 | 7 days | 50 mg/kg/day t.i.d | 8 (3 Nausea, 2 Dizziness, 1 Diarrhoea, 1 Unrest, 1 Feeling of heat |
| Manzato et al., 1995 | Unknown DRL | No | Retrospective | 30 | 30 | Up to 90 days | 7-17.5g/day | None |
| Maremmani et al., 2001 | VH DRL | No | Open | 35 | 35 | 12 months | 25-100 mg/kg | None |
| Mattila et al., 1978 – Study 1 | HV | No | Double-blind, cross-over, diazepam and placebo controlled | 12 | 12 | 1 day | 1 g unique dose | None |
| Mattila et al., 1978 – Study 2 | HV | No | Double-blind, cross-over, diazepam and placebo controlled | 12 | 12 | 4 x 2 days | 1g/2g/1g + alcohol | None |
| Moncini et al., 2000 Double-Blind | VH DRL | No | Double-blind, randomized | 17 | 9 | 6 months | 50 mg/kg/day t.i.d | 2 (Dizziness) |
| Moncini et al., 2000 Open 1 | VH DRL | No | Open | 22 | 22 | 6 days | 50-150 mg/kg/day t.i.d. | 2 (Diarrhoea) |
| Moncini et al., 2000 Open 2 | VH DRL | No | Open | 282 | 282 | 5 days | 50-100 mg/kg/day t.i.d. | 20 (Not specified) |
| Montesano et al., 1997 | Unknown DRL | No | Open | 51 | 51 | 3-6 months | 0.88-3.5g/day | None |
| Mosti & Zurla, 1995 – Arm 1 | Unknown DRL | No | Open | 28 | 28 | 9 days | 1.75g t.i.d | None |
| Mosti & Zurla, 1995 – Arm 2 | Unknown DRL | No | Open | 12 | 12 | 9 days | 1.75g q.i.d. | None |
| Mosti & Zurla, 1995 – Arm 3 | Unknown DRL | No | Open | 60 | 60 | 5 months | 4.2g/day t.i.d. | None |
| Nava et al., 2006 | VH DRL | No | Open, randomized | 86 | 28 | 12 months | 50 mg/kg/day t.i.d | 2 (Not specified) |
| Nava et al., 2007 | Unknown DRL | No | Open, Controlled | 21 | 21 | 21 days | 50 mg/kg/day q.i.d | None |
| Nava et al., 2017 – AWS | VH DRL | No | Retrospective | 485 | 18 | 41.3 days (± 28.4) | 77.1mg/kg/day (± 14.5) | 64 (Not specified) |
| VH DRL  + polydrugs addiction | Yes (polydrug users) | Retrospective | 485 | 205 | 41.3 days (± 28.4) | 77.1mg/kg/day (± 14.5) |
| VH DRL  + psychiatric comorbidities | Yes (patients with psychiatric comorbidities) | Retrospective | 485 | 131 | 41.3 days (± 28.4) | 77.1mg/kg/day (± 14.5) |
| Nava et al., 2017 – MoA | VH DRL | No | Retrospective | 485 | 4 | 218.4 (± 283.3) | 76.1 mg/kg/day (± 26.4) | None |
| VH DRL  + polydrugs addiction | Yes (polydrug users) | Retrospective | 485 | 88 | 218.4 (± 283.3) | 76.1 mg/kg/day (± 26.4) | None |
| VH DRL + psychiatric comorbidities | Yes (patients with psychiatric comorbidities) | Retrospective | 485 | 39 | 218.4 (± 283.3) | 76.1 mg/kg/day (± 26.4) | None |
| Nimmerrichter et al., 2002 – 50 mg/kg | Unknown DRL | No | Double-blind, clomethiazole controlled | 98 | 33 | 6 days | 50 mg/kg/day q.i.d. | 22 (17 Vertigo, 1 Nausea, 4 Diarrhoea) |
| Nimmerrichter et al., 2002 – 100 mg/kg | Unknown DRL | No | Double-blind, clomethiazole controlled | 98 | 32 | 6 days | 100 mg/kg/day q.i.d. | 37 (32 Vertigo, 1 Seizure, 2 Nausea, 2 Diarrhoea) |
| Oliveto et al., 2010 | HV | No | Double-blind, crossover | 17 | 17 | 8 x 1 day | 0; 0.32; 0.56; 0.75; 1.0; 1.8; 2.4; 3.2g/70kg | None |
| Palatini et al., 1993 | HV | No | Crossover | 8 | 8 | 3 x 1 day | 12.5 ; 25 and 50 mg/kg in one intake | 19 (Dizziness: 3 with 12.5mg/kg; 8 with 25 mg/kg and 8 with 50 mg/kg) |
| Stella et al., 2008 | VH DRL | No | Randomized | 48 | 0\* | 6 months | NA | NA |
| Strepparola et al., 1995 | VH DRL | No | Open | 76 | 76 | Up to 9 months | NR | None |
| Thai et al., 2006 | HV | No | Randomized, double-blind, 4-arm crossover | 16 | 16 | 2 x 1 day | 50 mg/kg in one intake | 2 (1 Vomiting, 1 Hypotension) |
| Vendramin and Bertuola, 1995 | Unknown DRL | No | NR | 6 | NR | NR | NR | None |
| Zolesi et al., 1995 | Unknown DRL | Yes (6 patients with craving for heroin) | Open/Case report | 26 | 26 | Up to 175 days | 2.63 – 10.5g/day t.i.d. | 21 (13 Vertigo, 7 Drowsiness, 1 Hyperammonaemia) |

DRL: Drinking Risk Level; L: Low; M: Medium; H: High; VH: Very High

HV: healthy volunteers

AWS: Alcohol Withdrawal Syndrome; MoA: Maintenance of Abstinence;

b.i.d.: twice a day; t.i.d.: three times a day; q.i.d.: four times a day;

NR: Not reported; NA: Not assessable

Combined data from [21 - 53, 55 - 62, 64, 65]