RECHERCHE CLINIQUE

Real-life use of baclofen for the treatment of alcohol dependence: results of a non-interventional Post-Authorization Safety Study in France

Utilisation du baclofène en vie réelle dans le traitement de la dépendance à l'alcool : résultats d'une étude de sécurité post-autorisation non interventionnelle menée en France

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Résumé

Contexte : La dépendance à l'alcool (DA) constitue un problème majeur de santé publique. En France, le baclofène est autorisé depuis 2018 pour réduire la consommation d'alcool chez les adultes présentant une DA avec une consommation d'alcool à haut risque, après échec des autres traitements. Cette étude a évalué sa sécurité d'utilisation en conditions de vie réelle sur une période de 12 mois.

Méthodes : Cette étude prospective, multicentrique, non interventionnelle de sécurité post-autorisation a été menée en France entre décembre 2020 et décembre 2024. Des adultes initiant un traitement par baclofène ont été suivis pendant une durée maximale de 12 mois dans le cadre de la pratique clinique courante.

Résultats : Parmi les 303 patients recrutés (278 traités), 72,3 % étaient des hommes et l'âge médian était de 47,5 ans. Le baclofène était prescrit pour une DA dans 98,6 % des cas. Les comorbidités étaient fréquentes (73,0 %), notamment la dépression majeure (45,8 %). La plupart des patients recevaient entre 30 et 80 mg/jour, sans dose dépassant 180 mg ; la durée médiane d'exposition était de 5,85 mois. Au cours des 12 mois, 45,0 % des patients ont présenté au moins un événement indésirable et 17,7 % un événement indésirable grave, dont seulement cinq ont été considérés comme liés au baclofène. Un décès, considéré comme non lié au traitement, est survenu et aucun nouveau signal de sécurité n'a été identifié. Parmi les patients pour lesquels des données de suivi étaient disponibles, des améliorations descriptives des scores AUDIT-C, du craving et de la CGI-S ont été observées au cours du temps. Seuls 100 des 301 patients inclus ont achevé le suivi à 12 mois ; 100 patients ont été perdus de vue.

Conclusion : Ces résultats confirment le profil de sécurité favorable du baclofène, en accord avec les données récentes de la littérature, sans identification de nouveau signal de sécurité.

Mots clés : dépendance à l'alcool, baclofène, événements indésirables, balance bénéfice-risque, efficacité, vie réelle.

Abstract

Background : Alcohol dependence (AD) is a major public health issue. In France, baclofen has been approved since 2018 to reduce alcohol consumption in adults with AD and high-risk drinking after treatment failure. This study assessed its safety in real-world conditions over 12 months.

Research design and methods : This prospective, multicenter, non-interventional post-authorization safety study was conducted in France between December 2020 and December 2024. Adults initiating baclofen were followed for up to 12 months in routine clinical practice.

Results : Among 303 enrolled patients (278 treated), 72.3% were male, with a median age of 47.5 years. Baclofen was prescribed for AD in 98.6% of cases. Comorbidities were frequent (73.0%), particularly major depression (45.8%). Most patients received 30–80 mg/day, with no dose exceeding 180 mg; median exposure was 5.85 months. Over 12 months, 45.0% experienced at least one adverse event and 17.7% a serious adverse event, with only five considered related to baclofen. One unrelated death occurred and no new safety signal was identified. Among patients with available follow-up data, descriptive improvements in AUDIT-C, craving and CGI-S were observed over time. Only 100 of the 301 included patients completed the 12-month follow-up; 100 patients were lost to follow-up.

Conclusion : These findings confirm the favorable safety profile of baclofen, consistent with recent literature, with no new safety concerns identified.

Key words : alcohol dependence, baclofen, adverse events, benefit-risk balance, effectiveness, real-life.

1. INTRODUCTION

Alcohol dependence (AD) is a major public health problem, accounting for approximately 2.6 million deaths worldwide in 2019 (1). Excessive alcohol consumption is associated with long-term consequences, including medical complications, mainly digestive, cardiovascular, oncological, and neuropsychiatric disorders, as well as psychological and social consequences (2). AD is generally considered the most severe stage of alcohol use disorder (AUD) and is the only stage for which pharmacotherapy is recommended to support abstinence or a reduction in alcohol consumption, in combination with appropriate psychosocial support (3). In a recent report, the French Observatory for Drugs and Addictive Trends indicated that 2023 was marked by a decrease in most indicators related to alcohol sales and consumption (4). Daily alcohol consumption among French adults declined by 13.0% between 2021 and 2023. Nevertheless, the number of alcohol-related hospital admissions increased in 2023 compared with 2022, with a rise of 4.1% in hospital stays and 2.5% in the number of patients.

Pharmacological treatments for AD aim to support patients in achieving either complete abstinence from alcohol or a substantial reduction in alcohol-related harm through decreased consumption, with both approaches shown to be beneficial (5). In France, between 2022 and 2023, the overall number of individuals receiving treatment for AD remained stable, although variations were observed according to the type of medication prescribed (4). Currently, five pharmacological treatments are available in France for the management of AD: acamprosate, indicated for the maintenance of abstinence; disulfiram, used as support for abstinence through its aversive effects; naltrexone, aimed at reducing craving and the risk of relapse; nalmefene, indicated for the reduction of alcohol consumption as part of a harm-reduction strategy; and baclofen (3). Management of AD also includes non-pharmacological interventions. These approaches aim to promote behavioral change, reduce or achieve cessation of alcohol use, prevent relapse, and support long-term psychosocial recovery. Several interventions are available, including brief interventions, motivational interviewing, and cognitive behavioral therapies, and are selected according to the severity of AD and individual patient needs (6).

Baclofen was approved in October 2018 and is indicated for the reduction of alcohol consumption in adult patients with AD who have high-risk alcohol use (more than 60 g/day for men and more than 40 g/day for women), after failure of other therapeutic options (7,8). Results across randomized controlled trials have been heterogeneous (9,10); nevertheless, many studies have reported reductions in alcohol consumption and craving and increases in the proportion of patients achieving abstinence or low-risk drinking with baclofen (11-13).

Following the marketing authorization of baclofen in France, real-world studies have provided valuable information regarding prescribing patterns, regulatory impacts, and clinical use in routine practice (14,15). However, few data have been generated from studies specifically designed to prospectively assess the safety profile of baclofen in routine clinical practice following its authorization. The present post-authorization safety study was therefore conducted at the request of the French Health Authority to further characterize the safety profile of baclofen in real-world settings. The objective was to describe the risks associated with baclofen use, as well as its safety outcomes and treatment exposure in routine clinical practice over a 12-month follow-up period.

2. PATIENTS AND METHODS

2.1. Study Design and subjects

This was a prospective, multicenter, non-comparative, non-interventional post-authorization safety study conducted in France between December 2020 and December 2024. Investigators were selected through a structured process designed to ensure representativeness and recruitment feasibility. Physicians were randomly sampled from the French National Health Insurance directory using stratification by specialty (psychiatrists, general practitioners) and geographical region, with additional physicians recruited from specialized addiction treatment centers. Overall, 30 centers across France participated in the study. Eligible patients were adults aged 18 years or older at enrolment for whom the investigator had decided to initiate baclofen treatment for the first time. However, given the observational nature of the study, actual treatment initiation remained at the patient's discretion, and some enrolled patients ultimately did not receive baclofen. Baclofen prescribing decisions were independent of study inclusion and aligned with the real-world

objectives of this study. Enrolled patients received treatment and clinical assessments as determined by their treating physicians, in accordance with local standard of care. Study visits were scheduled at the discretion of the physicians, based on patient-specific needs and routine clinical practice. Adverse events (AEs) were collected throughout the duration of the study, from initiation of treatment with baclofen until the final study evaluation. AE collection followed an active reporting approach: at each study visit, investigators systematically asked patients a non-leading question to identify any potential AEs, in addition to spontaneous reporting. The expected duration of study participation for each patient was up to 12 months.

2.2. Ethical approval procedure

The study protocol was reviewed and approved by the French Ethics Committee (EC) Île-de-France IV on May 22, 2020, prior to the inclusion of patients. The study was conducted in accordance with Good Epidemiological Practices and the French Public Health Code (in particular Article L.4113-6 and Decree No. 2007-454 of March 25, 2007). Data were collected in compliance with European Regulation 2016/679 (General Data Protection Regulation, GDPR) of April 27, 2016, and French Law No. 78-17 of January 6, 1978, on information technology, files and liberties amended. Patient names were not transmitted; only the site number and patient identification number were recorded in the electronic case report form (eCRF). Patients received both written and oral information about the study, and oral informed consent was obtained prior to the initiation of any study-related procedures.

2.3. Primary outcome

The primary outcome was the serious adverse events (SAEs) rate during the 12-month follow-up period.

2.4. Secondary outcomes

Secondary outcomes included description of:

- demographic and clinical characteristics of patients who received baclofen, including comorbidities and concomitant drugs;
- treatment with baclofen, including reasons for treatment initiation, dose modifications and reason for change(s);
- all SAEs (notably the hospitalizations and their reasons), including frequency and relationship to baclofen treatment;
- all AEs, including frequency, severity and relationship to baclofen treatment;
- change from baseline on Clinical Global Impression of Severity (CGI-S) according to the physician at approximately 1 month, 3 months, 6 months, 9 months and 1 year (Supplementary Methods);
- change from baseline on alcohol consumption using the Alcohol Use Disorders Identification Test for Consumption (AUDIT-C) questionnaire at approximately 1 month, 3 months, 6 months, 9 months and 1 year (Supplementary Methods);
- change from baseline on the craving using a 0-10 numeric rating scale (Supplementary Methods) at approximately 1 month, 3 months, 6 months, 9 months and 1 year.

2.5. Statistical analysis

Analysis populations were the following:

- Included population was defined as all patients having accepted to participate to the study,
- Safety population was defined as all patients who took at least one dose of baclofen.

Statistical analyses were performed using Statistical Analysis Systems (SAS®) release 9.4 (SAS institute, North Carolina, USA). The quantitative variables were summarized using the following parameters: number of non-missing data, number of missing data, mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum and maximum. Where applicable, the qualitative variables were summarized using the following parameters: number of non-missing data, number of missing data, counts and percentages. 95% confidence intervals (95% CI) of the frequency were presented where appropriate (Wald or Agresti-Coull for the categorical variables). Analyses were conducted on safety patient population (all patients who took at least one dose of baclofen).

3. RESULTS

3.1. Patients' disposition and baseline characteristics

Between December 20, 2020, and December 29, 2023, a total of 303 patients were consecutively enrolled during

consultations with participating physicians. Of these, two patients were considered screen failures and were excluded, resulting in 301 included patients. However, treatment initiation ultimately remained at the patient's discretion. Consequently, among the 301 included patients, 23 did not receive any dose of baclofen. The remaining 278 patients constituted the safety population (Figure 1). Of the 301 included patients, 100 (33.2%) completed the 12-month study follow-up. The main reasons for not completing the 12-month follow-up (n = 201) were loss to follow-up (49.8%), permanent discontinuation of baclofen (34.3%), and investigator's decision to discontinue treatment as per routine clinical practice (10.4%).

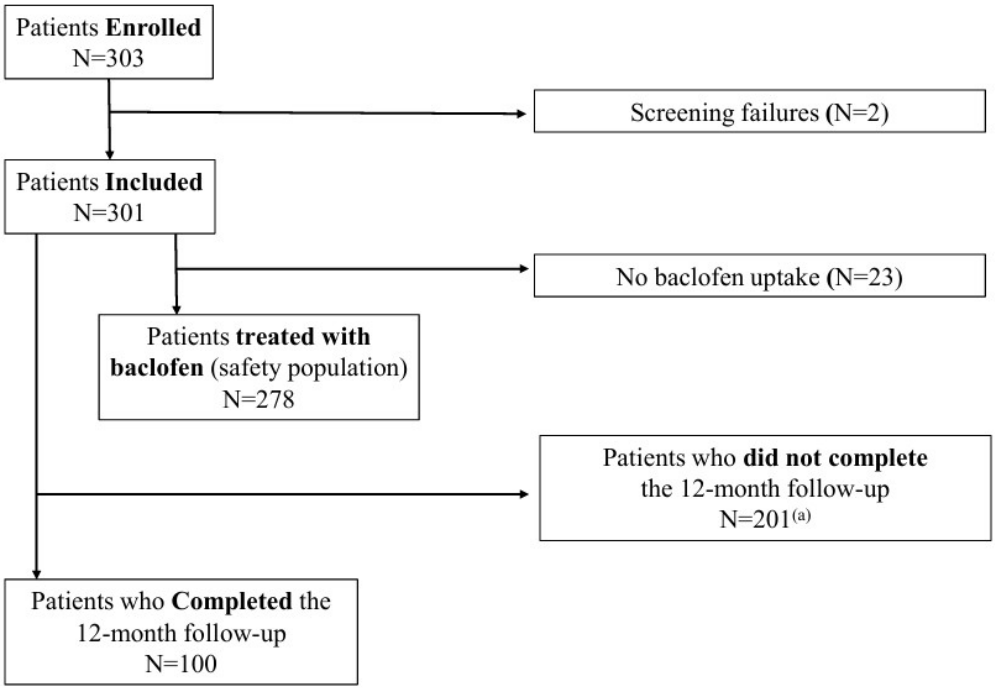

Figure 1. Flow diagram of patient disposition. Of the 303 enrolled patients, 301 were included and 278 received at least one dose of baclofen, constituting the safety population. Among the 301 included patients, 100 completed the 12-month follow-up and 201 did not complete the study. (a) The main reasons for non-completion were loss to follow-up (n=100), permanent discontinuation of baclofen (n=69), and investigator's decision (n=21).

Patients' baseline characteristics are presented in Table 1. The median age of the 278 patients included in the safety population was 47.5 years (range: 19.0–81.0), and the majority were male (72.3%). Baclofen was prescribed for AD in 274 patients (98.6%). In the remaining four patients, baclofen was prescribed for compulsive alcohol intake (n = 3) and anorexia/ bulimia (n = 1), reflecting the real-world nature of this non-interventional study. Comorbidities were common, affecting 73.0% of patients, with major depressive disorder (45.8%) and other psychiatric disorders (42.8%) being the most frequently reported. Overall, 68.3% of patients received at least one concomitant treatment. The median duration of study participation was 6.64 months (range: 0–15.2 months).

		Total N = 278
Age at inclusion (years)	Mean ± SD	47.96 ± 11.69
	Median	47.50
	Min ; Max	19.0 ; 81.0
Age groups at inclusion (years)	18–34	33 (11.9%)
	35–49	129 (46.4%)
	50–64	91 (32.7%)
	≥65	25 (9.0%)
Gender, Male		201 (72.3%)
Weight (kg)	Mean ± SD	76.79 ± 17.00
	Median	75.00

		Total N = 278
	Min ; Max	45.0 ; 130.0
BMI (kg/m²)	Mean ± SD	25.42 ± 4.63
	Median	24.82
	Min ; Max	15.6 ; 42.0
Reason for baclofen prescription	Alcohol dependence	**274** (98.6%)
Family history of alcohol dependence		172 (62.8%)
Age of onset of alcohol use problems (years)	<30	144 (52.6%)
	30-39	73 (26.6%)
	40-49	36 (13.1%)
	50-59	11 (4.0%)
	60-69	9 (3.3%)
Patients with at least one ongoing comorbidity		**203** (73.0%)
Major depression		93 (45.8%)
Psychiatric disorders other than depression		87 (42.8%)
Patients with at least one concomitant treatment at baseline		**190** (68.3%)
Number of concomitant treatments per patient	Mean ± SD	2.94 ± 2.11
	Median	2.00
	Min ; Max	1.0 ; 14.0
Psycholeptics		115 (60.5%)
Psychoanaleptics		85 (44.7%)
Other Nervous System Drugs		45 (23.7%)
Study duration (months)	N (mv)	275 (3)
	Mean ± SD	6.95 ± 4.49
	Median	6.64
	Min ; Max	0.0 ; 15.2

Table 1. Patients' baseline characteristics

Data are n (%), and Mean ± SD. SD: Standard Deviation. mv: missing values.

3.2. Exposure to Baclofen

The median initially prescribed daily dose of baclofen was 20 mg (range: 10–80 mg). At treatment initiation, 173 of the 278 patients in the safety population (62.2%) were prescribed a daily dose below 30 mg. An alcohol consumption target at inclusion was documented for 271 patients (97.5%): 169 patients (62.4%) aimed to reduce alcohol consumption, while 102 patients (37.6%) aimed for abstinence (Table 2). Over the course of the study, most patients received a mean baclofen dose ranging from 30 mg up to but not including 80 mg from first intake (n = 173; 64.3%). Fifty-two patients (19.3%) received a mean dose of less than 30 mg, and 44 patients (16.4%) received mean doses ranging from 80 mg up to but not including 180 mg. No patient had a mean daily dose of 180 mg/day or higher. Thus, mean baclofen doses remained well below the maximum recommended daily dose of 300 mg throughout the study. Mean dose data were missing for nine patients. Overall, 247 patients (88.8%) underwent at least one baclofen dose modification, most frequently involving upward titration. Details regarding dose adjustments are provided in Supplementary Table 1.
The median duration of exposure to baclofen was 5.85 months (range: 0–13.8 months) among 269 patients; exposure data were missing for nine patients (Table 2).

		Total N = 278
Initial prescribed daily dose (mg)	Mean ± SD	25.49 ± 9.98
	Median	20.00
	Min ; Max	10.0 ; 80.0
Initial prescribed daily dose (mg) (classes)	<30	173 (62.2%)
	30-79	104 (37.4%)
	80-180	1 (0.4%)
Definition of an alcohol consumption target at inclusion		**271** (97.5%)
Reduction of alcohol consumption		169 (62.4%)
Abstinence		102 (37.6%)
Range of dose of baclofen [a]	N (mv)	269 (9)
	<30	52 (19.3%)
	30-79	173 (64.3%)
	80-180	44 (16.4%)
At least one baclofen dose modification		247 (88.8%)
Total number of dose modifications		**1205**
Increase of dose		916 (76.0%)
Dose increase for titration		803 (68.2%)*
Exposure to baclofen (months)	N (mv)	269 (9)
	Mean ± SD	6.50 ± 4.49
	Median	5.85
	Min ; Max	0.0 ; 13.8

Table 2. Baclofen initiation and exposure

Data are n (%) or mean ± SD; mv: missing values.
[a] Range dose of baclofen: mean dose of baclofen since the first intake.
* Reasons for dose modification were reported for 1178 dose modifications (missing for 27).

3.3. Incidence rate of Serious Adverse Events - Primary endpoint of the study

The incidence of SAEs, which constituted the primary endpoint of the study, during the 12-month follow-up period is summarized in Table 3. Among the 278 patients in the safety population, 28 patients (10.1%) experienced at least one SAE during follow-up, and a total of 52 SAEs were reported. The corresponding SAE incidence rate was 17.7% per person-year (95% CI: 12.20%-25.59%).
Of these, five patients (1.8%) experienced at least one SAE considered related to baclofen. Detailed descriptions of these five patients are provided in Table 4. These events included one patient with deliberate poisoning; one patient with suicidal ideation; one patient with anxiety; one patient with abdominal pain upper; and one patient with glaucoma.

	Total N = 278
Number of patients with SAEs during the 12-month follow-up period	28 (10.1%)
Total number of SAEs	52
Incidence rate per person-years [95% CI]	17.7% [12.20%;25.59%]

Table 3. Incidence rate of Serious Adverse Events during the 12-month follow-up period.

Data are n (%); SAEs, serious adverse events.

3.4. All Adverse Events

Overall, during the study period, 125 patients (45.0%) reported a total of 278 AEs. Among them, 57 patients experienced AEs unrelated to baclofen treatment, while 92 patients reported AEs considered related to

baclofen (Table 4 and Supplementary Table 2). AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs). Among the 92 patients who experienced baclofen-related AEs, the most frequently reported events involved nervous system disorders, which were reported by 53 patients (57.6%). These included somnolence (n = 22; 23.9%), sedation (n = 16; 17.4%), and dizziness (n = 11; 12.0%). Gastrointestinal disorders were reported by 22 patients (23.9%), including nausea (n = 9; 9.8%) and diarrhea (n = 7; 7.6%). General disorders and administration site conditions were reported by 14 patients (15.2%), mainly fatigue (n = 7; 7.6%). Psychiatric symptoms were reported by 16 patients (17.4%), including loss of libido (3.3%), anxiety (2.2%), and suicidal ideation (2.2%) (Table 4).

	Total N = 278
Any AE	125 (45.0%) [278]
Any severe AE	23 (8.3%) [42]
Any related AE (most frequent)	92 (33.1%) [171]
Nervous system disorders	**53 (57.6%)**
Somnolence	22 (23.9%)
Sedation	16 (17.4%)
Dizziness	11 (12.0%)
Gastrointestinal disorders	**22 (23.9%)**
Nausea	9 (9.8%)
Diarrhea	7 (7.6%)
General disorders and administration site conditions	**14 (15.2%)**
Fatigue	7 (7.6%)
Psychiatric disorders	**16 (17.4%)**
Loss of libido	3 (3.3%)
Anxiety	2 (2.2%)
Suicidal ideation	2 (2.2%)
Any serious AE related to baclofen	5 (1.8%)
Injury, poisoning and procedural complications	**1 (20.0%)**
Deliberate poisoning	1 (20.0%)
Psychiatric disorders	**2 (40.0%)**
Suicidal ideation	1 (20.0%)
Anxiety	1 (20.0%)
Gastrointestinal disorders	**1 (20.0%)**
Abdominal pain upper	1 (20.0%)
Eye disorders	**1 (20.0%)**
Glaucoma	1 (20.0%)

Table 4. Adverse Events occurring during the 12-month follow-up period.

Data are n (%); [E], events; AEs, adverse events. Adverse events were classified according to the MedDRA SOCs.

Among the 278 patients included, 22 (7.9%) experienced at least one hospitalization during the study period. Overall, 39 events resulted in 29 hospitalizations among these 22 patients (Table 5). The most common reasons for hospitalization were falls, cerebral trauma and fractures, alcohol intoxication, alcohol withdrawal, and psychiatric SAEs. All hospitalized patients had recovered by the end of the study. The distribution of SAEs according to baclofen dose is presented in Supplementary Table 3. One death occurred during the study period. The patient died following a fall from a height of four to five floors, in an unknown context, resulting in multiple injuries. The patient was receiving antidepressant and anxiolytic medications and had no reported history of suicide attempts, suicidal ideation, or substance use disorders other than alcohol and nicotine. This event occurred approximately one month after initiation of baclofen treatment. Information regarding the last baclofen dose and the date of last intake before the event was not collected. According to the treating physician, the fatal fall was considered unrelated to baclofen and attributed instead to a pre-existing anxio-depressive syndrome.

	Total N = 278
At least one hospitalization during the 12-month follow-up period	22 (7.9%) [29]
Total number of events having led to a hospitalization	39
Patients hospitalised due to fall, cerebral trauma and fractures	6 (27.3%) [10]
Patients hospitalised due to alcohol intoxication	4 (18.2%) [7]
Patients hospitalised due to alcohol withdrawal	3 (13.6%) [3]
Patients hospitalised due to psychiatric SAE (increase in mood disorders, anxiety and suicidal thoughts)	3 (13.6%) [3]
Patients hospitalised due to acute pancreatitis	2 (9.1%) [2]
Patients hospitalised due to voluntary drug intoxication	2 (9.1%) [2]
Patients hospitalised due to a respiratory SAE (decompensation of an obstructive respiratory failure)	1 (4.5%) [1]
Patients hospitalised due to general status alteration	1 (4.5%) [1]

Table 5. Hospitalizations during the 12-month follow-up period.

Data are n or n (%); [H], hospitalizations.

3.5. Clinical effectiveness of baclofen

3.5.1. Clinical global impression of severity

The Clinical Global Impression–Severity scale (CGI-S) was used at the inclusion visit to assess the severity of AD in the 278 patients who received at least one dose of baclofen. One patient was not assessed. At baseline, 23 patients were rated as "normal, not at all ill", while 131 patients (47.1%) were classified as "borderline, mildly, or moderately ill". Notably, more than one third of the cohort (n = 123; 44.2%) was rated as "markedly or severely ill", and four patients were considered among the "most extremely ill" at study entry. Over the course of the study, improvements in CGI-S ratings were observed among patients who attended follow-up visits from 1 to 12 months. The proportion of patients rated as "normal, not at all ill" increased from 8.3% at inclusion (among 278 patients) to 27.1% at the 12-month visit (among 85 patients). Similarly, the proportions of patients rated as "borderline" and "mildly ill" increased from 14.5% to 34.1% and from 9.4% to 15.3%, respectively. In contrast, the proportions of patients rated as "moderately ill", "markedly ill", and "severely ill" decreased substantially over time, from 22.8% to 10.6%, from 28.6% to 9.4%, and from 14.4% to 1.2%, respectively, between the inclusion visit and the 12-month follow-up (Supplementary Figure 1). The number of patients classified as most extremely ill remained very low throughout the study period. Changes from baseline in CGI-S scores were evaluated at each follow-up visit (Table 6). No change was observed at the 1-month visit. From the 3-month visit onward, progressive improvements were noted, with median CGI-S scores decreasing by 16.7%, 20.0%, 20.0%, and 33.3% at the 3-, 6-, 9-, and 12-month visits, respectively, compared with baseline (Table 6).

3.5.2. Alcohol use disorders identification test for consumption

The Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) questionnaire was administered at each follow-up visit. Over the study period, among patients who completed at least one follow-up visit between 1 and 12 months, the proportions of patients reporting a high frequency of drinks containing alcohol, elevated number of standard drinks containing alcohol on an ordinary day and high frequency of six or more drinks during the same occasion progressively decreased (Supplementary Figure 2). Changes from baseline in total score (sum of the three items) were evaluated at each follow-up visit (Table 6). At the 1-month visit, a median relative decrease of 23.6% from baseline was observed. From the 3-month visit onwards, sustained reductions in AUDIT-C total scores were noted, with median decreases of 33.3%, 36.4%, 27.3%, and 54.5% at the 3-, 6-, 9-, and 12-month visits, respectively, compared with baseline.

3.5.3. Craving for alcohol

Craving for alcohol during the previous 7 days was assessed at each follow-up visit using a numerical rating scale ranging from 0 (no craving) to 10 (maximal craving). Analyses were conducted among patients who completed at least one follow-up visit, with comparisons made to baseline values. Median craving scores progressively decreased over the study period, from 7 at inclusion to 3 at the 12-month visit (Supplementary Figure 3). Changes from baseline in craving scores were evaluated at each follow-up visit (Table 6). At the 1-month visit, a median relative decrease of 20.0% from baseline was observed. From the 3-month visit onwards, further reductions were noted, with median decreases of 30.0%, 40.0%, 40.0%, and 50.0% at the 3-,

6-, 9-, and 12-month visits, respectively, compared with baseline.

		At 1 month N=245	At 3 months N=205	At 6 months N=146	At 9 months N=119	At 12 months N=85
Relative change of CGI-S from baseline (%)	N (mv)	244 (1)	204 (1)	146	119	85
	Mean ± SD	-7.34 ± 39.16	-16.33 ± 40.70	-22.93 ± 37.34	-24.97 ± 38.18	-30.51 ± 41.37
	Median	0.00	-16.67	-20.00	-20.00	-33.33
	Min ; Max	-100.0 ; 300.0	-100.0 ; 200.0	-83.3 ; 100.0	-100.0 ; 100.0	-83.3 ; 100.0
Relative change of AUDIT-C total score from baseline (%)	N (mv)	238 (7)	191 (14)	129 (17)	109 (10)	79 (6)
	Mean ± SD	-28.1 ± 40.6	-33.0 ± 53.7	-35.7 ± 58.7	-30.6 ± 80.6	-44.8 ± 72.4
	Median	-23.6	-33.3	-36.4	-27.3	-54.5
	Min ; Max	-100 ; 267	-100 ; 400	-100 ; 400	-100 ; 600	-100 ; 500
Relative change of craving for alcohol from baseline (%)	N (mv)	243 (2)	203 (2)	145 (1)	118 (1)	84 (1)
	Mean ± SD	-20.7 ± 49.4	-26.2 ± 74.3	-39.2 ± 38.8	-36.1 ± 48.7	-49.6 ± 44.7
	Median	-20.0	-30.0	-40.0	-40.0	-50.0
	Min ; Max	-100 ; 300	-100 ; 600	-100 ; 100	-100 ; 200	-100 ; 150

Table 6. Clinical effectiveness of baclofen treatment

Data are mean ± SD; mv: missing values; AUDIT-C, alcohol use disorders identification test for consumption.
Relative change from baseline: 100*(value of the parameter at follow-up – value of the parameter at inclusion)/value of the parameter at inclusion. Note: a value may be missing from Relative change calculation, if baseline parameter value was 0. Timepoints were proposed as illustrative reference and did not constitute mandatory or predefined visit windows.

4. DISCUSSION

This study included 303 patients among whom 278 received baclofen for the treatment of AD. The demographic and clinical characteristics of the study population were consistent with those commonly reported in patients with AD. The influence of risk factors—including genetic, familial, health-related, and psychosocial factors—appears to vary according to age and gender (16, 17). Moreover, 73.0% of patients treated with baclofen presented with at least one comorbidity at baseline, the most frequent being major depression (45.8%). These findings are consistent with the comorbidity profile typically described in patients with AUD (18). Furthermore, the co-occurrence of major depressive disorder in individuals entering treatment for AD has been associated with increased morbidity and mortality and may adversely affect treatment outcomes (19). Regarding baclofen exposure, the mean daily dose was below 80 mg in most patients (83.6%), and no patient had a mean dose of 180 mg/day or higher. The median duration of baclofen exposure was 5.85 months.

Our results showed that, over the study period, 125 patients (45.0%) reported a total of 278 AEs, predominantly involving the nervous system, the gastrointestinal system, and psychiatric disorders. Most reported AEs occurred in patients receiving low-dose baclofen, which is consistent with the predominance of low-dose exposure in the study population and should not be interpreted as evidence of lower dose-related risk. The most frequently reported AEs in our study were somnolence and sedation. These findings are consistent with a recent systematic review and dose–response meta-analysis of 14 clinical trials (n=1344 patients) (20) as well as with a Cochrane systematic review of baclofen in AUD including 17 randomized trials (n=1818 participants) (21).

In our study, the incidence rate of SAEs during the 12-month follow-up period was 17.7%. Among the 278 patients included in the safety population, only a small proportion (7.9%) experienced at least one hospitalization during the study period. This rate is lower than the 12.7% hospitalization rate reported in the French cohort study published in 2018 (22). Notably, only one death was reported in our study, resulting from a fall associated with multiple injuries. Information regarding the last baclofen dose and the date of last intake prior to this SAE was not available. According to the attending physician, this fatal event was

considered unrelated to baclofen treatment.
This study has two main limitations. First, due to the observational, non-comparative study design, the results regarding the clinical effectiveness of baclofen should be considered descriptive trends only. In addition, the number of patients attending follow-up visits progressively decreased over time, from 278 at inclusion to 85 at the 12-month visit. Nevertheless, despite this attrition, a consistent trend toward clinical improvement was observed throughout the follow-up period. This was particularly evident in the decreasing number of patients classified as "most extremely ill" during follow-up. Accordingly, CGI-S scores showed reductions from baseline across visits, with only a very small number of patients remaining in the "most extremely ill" category at the end of the study, while the proportion of patients rated as "normal or not at all ill" increased from inclusion to the 12-month visit. Similar improvements were observed for alcohol consumption and craving outcomes, as reflected by progressive decreases in AUDIT-C total scores and self-reported craving for alcohol up to the 12-month visit. The second limitation relates to the proportion of patients lost to follow-up (LFU; n = 100) and the lack of corresponding follow-up data. This limitation was anticipated, given the challenge of maintaining long-term follow-up and study participation among patients with AUD in routine care setting. To address this issue, a second retrospective phase is planned, during which data from LFU patients will be linked to the French nationwide medico-administrative database (SNDS). This linkage will allow further characterization of these patients, including their characteristics, vital status, and safety outcomes. Information on relevant treatments (including baclofen, psychiatric medications, and other treatments for AD), hospitalizations, and pregnancy will be examined. Access to the exhaustive SNDS data for LFU patients is expected to further strengthen and complete the safety profile of baclofen.

5. CONCLUSIONS

In this 12-month, prospective, multicenter, non-interventional post-authorization safety study conducted in France, 303 patients were enrolled, of whom 278 received baclofen for the treatment of AD. Overall, baclofen was well tolerated, with a low proportion of treatment-related SAEs, and no new or unexpected safety signals were identified. These findings are consistent with those reported in recent systematic reviews and meta-analyses (20,21). Although the relatively high proportion of patients lost to follow-up warrants cautious interpretation, these results provide valuable real-world evidence supporting the safety profile of baclofen in routine clinical practice.

Data availability statement : This study was conducted under a post-authorization commitment with the French health authorities. Consequently, the datasets generated during the current study are not publicly available due to regulatory and legal constraints.
Conflicts of interest : NS is or was member of advisory boards, DSMB, or steering committees for Bioprojet, and Ethypharm, and has received sponsorship to attend scientific meetings, speaker honoraria or consultancy fees from Ethypharm, Kinnov Pharmaceuticals, Aelis Farma, and Lundbeck. HJA is or was member of advisory boards, DSMB, or steering committees for Bioprojet, Eos, and Ethypharm, and has received sponsorship to attend scientific meetings, speaker honoraria or consultancy fees from 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 past 36 months, by Lilly, Imbrium, Alkermes, Dicerna, Ethypharm, Indivior, Kinnov Therapeutics, Otsuka, and Pear Therapeutics. BT received fees for lectures and consultancy from Ethypharm. CG has participated in clinical studies sponsored by AbbVie, Gilead, Ethypharm and Indivior. PC: none. MO and BZ are employees of Ethypharm.
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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY METHODS (CLINICAL ASSESSMENTS)

Clinical global impression of severity:

Considering your total clinical experience with this particular population, how you do you assess the disease severity of the patient's current alcohol use?

○ Not evaluated

○ Normal, not at all ill

○ Borderline mentally ill

○ Mildly ill

○ Moderately ill

○ Markedly ill

○ Severely ill

○ Among the most extremely ill patients

AUDIT-C questionnaire:

1. How often do you have a drink containing alcohol?

○ Never

○ Monthly or less

○ 2 - 4 times a month

○ 2 - 3 times a week

○ 4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day?

○ 1 or 2

○ 3 or 4

○ 5 or 6

○ 7 to 9

○ 10 or more

3. How often do you have six or more drinks on one occasion?

○ Never

○ Less than monthly

○ Monthly

○ Weekly

○ Daily or almost daily

Numeric scale of craving:

On a scale from 0 to 10, 0 being 'None at all' and 10 being 'extreme', could you qualify how strong your craving for alcohol was during the last 7 days?

|__|__|/ 10

SUPPLEMENTARY RESULTS

Supplementary Tables

Supplementary Table 1. Dose modifications and interruptions (Safety population, N = 278).

		Total N = 278
At least one dose modification	N	278

		Total N = 278
	No	31 (11.2%)
	Yes	247 (88.8%)
If at least one dose modification,		
Type of dose modification *	N	1205
	Decrease	289 (24.0%)
	Increase	916 (76.0%)
Reason for dose modification *	N (mv)	1178 (27)
	Titration	803 (68.2%)
	Overdose	13 (1.1%)
	Alcohol consumption target not achieved	197 (16.7%)
	Therapeutic decrease (target achieved)	63 (5.3%)
	AE	102 (8.7%)
At least one temporary discontinuation	N	278
	No	251 (90.3%)
	Yes	27 (9.7%)
If at least one temporary Baclocur® discontinuation,		
Number of temporary discontinuations	N	27
	Mean ± SD	1.11 ± 0.32
	Median	1.00
	Min ; Max	1.0 ; 2.0
Number of temporary discontinuations per patient (classes)	N	27
	1	24 (88.9%)
	2	3 (11.1%)
Number of temporary discontinuations	N	30
Reason for temporary discontinuation	N (mv)	17 (13)
	Titration	3 (17.6%)
	Alcohol consumption target not achieved	2 (11.8%)
	Therapeutic decrease (target achieved)	2 (11.8%)
	AE	10 (58.8%)
Duration of temporary discontinuation (months) [a]	N (mv)	24 (6)
	Mean ± SD	1.11 ± 0.89
	Median	0.82
	Min ; Max	0.1 ; 3.2
Total duration of temporary discontinuations (months) [b]	N (mv)	21 (6)
	Mean ± SD	1.27 ± 1.03
	Median	0.76
	Min ; Max	0.1 ; 3.2
Permanent Baclocur® discontinuation	N	278
	No	210 (75.5%)
	Yes	68 (24.5%)

		Total N = 278
If Yes, duration of treatment with Baclocur® (months) [c]	N	68
	Mean ± SD	4.62 ± 2.98
	Median	4.32
	Min ; Max	0.3 ; 11.7
Exposure to Baclocur® (months) [d]	N (mv)	269 (9)
	Mean ± SD	6.50 ± 4.49
	Median	5.85
	Min ; Max	0.0 ; 13.8

Results are presented as n (%) or mean ± SD; SD: Standard Deviation. mv, missing values.
Note: Data was from pages Treatment by Baclocur®.
*A patient could have several dose modifications and/or several temporary Baclocur® discontinuations
[a] Duration of one temporary discontinuation: (date of Baclocur® restarted – date of Baclocur® temporarily discontinued) / 30.4375
[b] Total duration of temporary discontinuations: sum of all durations on temporary discontinuations
[c] Duration of treatment with Baclocur®: (date of permanent Baclocur® discontinuation – date of first intake of Baclocur®) / 30.4375
[d] Exposure to Baclocur®: [(date of last Baclocur® intake – date of first intake of Baclocur®) – sum of all temporary discontinuations] / 30.4375. In case of ongoing treatment at the time of evaluation the date of visit was considered as the date of last Baclocur® intake.

Supplementary Table 2. Adverse Events by System Organic Class and Preferred Term and according to relation to treatment – Safety population (N = 278)

		Not related N = 57	Related N = 92
Number of patients with at least one AE		57 (100.0%)	92 (100.0%)
Nervous system disorders		11 (19.3%)	53 (57.6%)
	Somnolence	4 (7.0%)	22 (23.9%)
	Sedation		16 (17.4%)
	Dizziness	1 (1.8%)	11 (12.0%)
	Headache	2 (3.5%)	4 (4.3%)
	Disturbance in attention		5 (5.4%)
	Paraesthesia	1 (1.8%)	2 (2.2%)
	Memory impairment	1 (1.8%)	1 (1.1%)
	Ageusia		1 (1.1%)
	Amnesia		1 (1.1%)
	Balance disorder		1 (1.1%)
	Coma	1 (1.8%)	
	Dysgeusia		1 (1.1%)
	Epilepsy	1 (1.8%)	
	Idiopathic generalised epilepsy	1 (1.8%)	
	Tremor		1 (1.1%)
Gastrointestinal disorders		11 (19.3%)	22 (23.9%)
	Nausea		9 (9.8%)
	Diarrhoea	1 (1.8%)	7 (7.6%)
	Dry mouth		4 (4.3%)
	Abdominal pain upper	2 (3.5%)	1 (1.1%)
	Constipation		2 (2.2%)

		Not related N = 57	Related N = 92
	Gastritis	2 (3.5%)	
	Toothache	2 (3.5%)	
	Abdominal discomfort		1 (1.1%)
	Abdominal pain	1 (1.8%)	
	Alcoholic pancreatitis	1 (1.8%)	
	Dyspepsia		1 (1.1%)
	Oesophageal varices haemorrhage	1 (1.8%)	
	Pancreatitis	1 (1.8%)	
	Pancreatitis acute	1 (1.8%)	
	Paraesthesia oral		1 (1.1%)
	Rectal haemorrhage		1 (1.1%)
	Salivary hypersecretion		1 (1.1%)
	Vomiting	1 (1.8%)	
General disorders and administration site conditions		11 (19.3%)	14 (15.2%)
	Fatigue	1 (1.8%)	7 (7.6%)
	Asthenia	2 (3.5%)	3 (3.3%)
	Feeling abnormal	1 (1.8%)	3 (3.3%)
	General physical health deterioration	2 (3.5%)	
	Alcohol interaction	1 (1.8%)	
	Drug ineffective	1 (1.8%)	
	Impaired healing	1 (1.8%)	
	Malaise	1 (1.8%)	
	Multiple organ dysfunction syndrome	1 (1.8%)	
	Thirst		1 (1.1%)
Psychiatric disorders		11 (19.3%)	16 (17.4%)
	Anxiety	1 (1.8%)	2 (2.2%)
	Depression	2 (3.5%)	1 (1.1%)
	Loss of libido		3 (3.3%)
	Suicidal ideation	1 (1.8%)	2 (2.2%)
	Affective disorder	2 (3.5%)	
	Anorgasmia	1 (1.8%)	1 (1.1%)
	Nightmare		2 (2.2%)
	Sleep disorder		2 (2.2%)
	Abnormal dreams		1 (1.1%)
	Agitation		1 (1.1%)
	Alcohol withdrawal syndrome	1 (1.8%)	
	Alcoholism	1 (1.8%)	
	Confusional state		1 (1.1%)
	Depressed mood		1 (1.1%)
	Drug dependence	1 (1.8%)	

		Not related N = 57	Related N = 92
	Grief reaction	1 (1.8%)	
	Hallucination, visual		1 (1.1%)
	Libido decreased	1 (1.8%)	
	Libido disorder	1 (1.8%)	
	Mood swings		1 (1.1%)
	Persistent depressive disorder		1 (1.1%)
	Suicide attempt	1 (1.8%)	
	Terminal insomnia		1 (1.1%)
Injury, poisoning and procedural complications		16 (28.1%)	3 (3.3%)
	Alcohol poisoning	6 (10.5%)	1 (1.1%)
	Fall	7 (12.3%)	
	Poisoning deliberate	1 (1.8%)	1 (1.1%)
	Wrist fracture	2 (3.5%)	
	Cervical vertebral fracture	1 (1.8%)	
	Clavicle fracture	1 (1.8%)	
	Concussion	1 (1.8%)	
	Head injury	1 (1.8%)	
	Ligament rupture	1 (1.8%)	
	Multiple injuries	1 (1.8%)	
	Product dose omission in error	1 (1.8%)	1 (1.1%)
Ear and labyrinth disorders		1 (1.8%)	8 (8.7%)
	Tinnitus	1 (1.8%)	4 (4.3%)
	Vertigo		4 (4.3%)
Musculoskeletal and connective tissue disorders		4 (7.0%)	5 (5.4%)
	Myalgia	2 (3.5%)	2 (2.2%)
	Muscle spasms		2 (2.2%)
	Pain in extremity	2 (3.5%)	
	Arthralgia		1 (1.1%)
	Back pain	1 (1.8%)	
	Neck pain	1 (1.8%)	
	Tendon pain	1 (1.8%)	
Skin and subcutaneous tissue disorders		1 (1.8%)	8 (8.7%)
	Hyperhidrosis	1 (1.8%)	6 (6.5%)
	Dry skin		1 (1.1%)
	Night sweats		1 (1.1%)
	Rash		1 (1.1%)
Infections and infestations		7 (12.3%)	
	COVID-19	3 (5.3%)	
	Erysipelas	1 (1.8%)	

		Not related N = 57	Related N = 92
	Pneumonia	1 (1.8%)	
	Pneumonia aspiration	1 (1.8%)	
	Tooth infection	1 (1.8%)	
Metabolism and nutrition disorders		1 (1.8%)	4 (4.3%)
	Decreased appetite		3 (3.3%)
	Appetite disorder		1 (1.1%)
	Diabetes mellitus	1 (1.8%)	
Eye disorders		1 (1.8%)	3 (3.3%)
	Dry eye		1 (1.1%)
	Glaucoma		1 (1.1%)
	Vision blurred	1 (1.8%)	
	Visual field defect		1 (1.1%)
Reproductive system and breast disorders			4 (4.3%)
	Erectile dysfunction		2 (2.2%)
	Intermenstrual bleeding		1 (1.1%)
	Sexual dysfunction		1 (1.1%)
Respiratory, thoracic and mediastinal disorders		2 (3.5%)	1 (1.1%)
	Acute respiratory failure	1 (1.8%)	
	Dry throat		1 (1.1%)
	Nasal dryness		1 (1.1%)
	Obstructive sleep apnoea syndrome	1 (1.8%)	
Renal and urinary disorders		1 (1.8%)	1 (1.1%)
	Acute kidney injury	1 (1.8%)	
	Pollakiuria		1 (1.1%)
Surgical and medical procedures		2 (3.5%)	
	Alcohol detoxification	1 (1.8%)	
	Therapy interrupted	1 (1.8%)	
Vascular disorders		1 (1.8%)	1 (1.1%)
	Hot flush	1 (1.8%)	1 (1.1%)
Cardiac disorders		1 (1.8%)	
	Atrial fibrillation	1 (1.8%)	
	Cardiac flutter	1 (1.8%)	
	Supraventricular tachycardia	1 (1.8%)	
Investigations			1 (1.1%)
	Weight increased		1 (1.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1 (1.8%)	
	Neoplasm malignant	1 (1.8%)	

Results are presented as n (%). Patients are counted only once per primary SOC and PT. A patient can have several AEs with different relations to treatment.

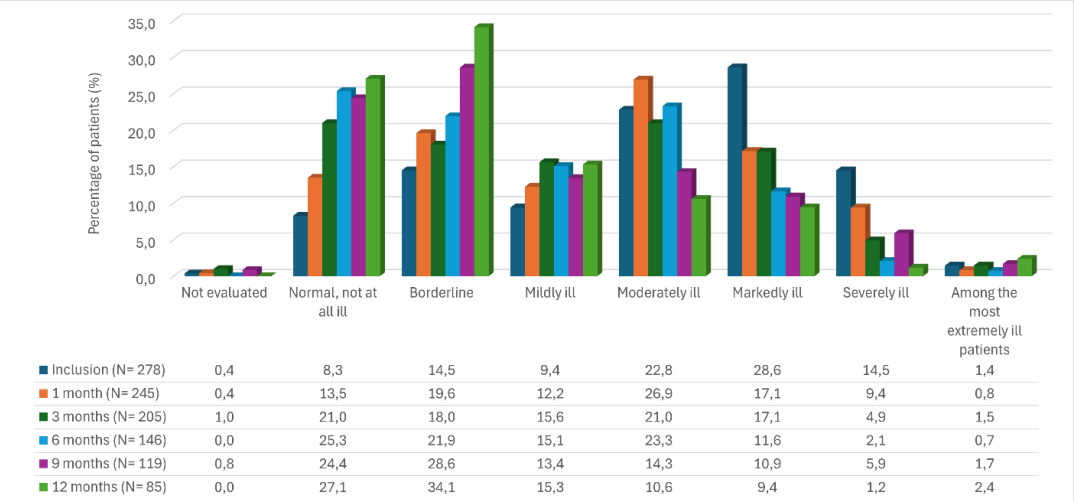
Supplementary Table 3. Serious Adverse Events by System Organic Class and Preferred Term and according to the range of dose of Baclocur® (in mg/day) – Safety population (N = 278).

		<30 N = 52	[30-80[N = 173	[80-180[N = 44
Number of patients with at least one SAE		3 (5.8%)	17 (9.8%)	7 (15.9%)
Injury, poisoning and procedural complications		2 (66.7%)	7 (41.2%)	4 (57.1%)
	Fall		4 (23.5%)	1 (14.3%)
	Alcohol poisoning	1 (33.3%)	2 (11.8%)	1 (14.3%)
	Poisoning deliberate	1 (33.3%)		1 (14.3%)
	Cervical vertebral fracture		1 (5.9%)	
	Clavicle fracture			1 (14.3%)
	Concussion			1 (14.3%)
	Head injury		1 (5.9%)	
	Ligament rupture		1 (5.9%)	
	Wrist fracture		1 (5.9%)	
Psychiatric disorders			5 (29.4%)	1 (14.3%)
	Suicidal ideation		2 (11.8%)	
	Affective disorder		1 (5.9%)	
	Alcohol withdrawal syndrome			1 (14.3%)
	Alcoholism		1 (5.9%)	
	Anxiety		1 (5.9%)	
	Drug dependence			1 (14.3%)
	Suicide attempt			1 (14.3%)
Gastrointestinal disorders			4 (23.5%)	1 (14.3%)
	Abdominal pain		1 (5.9%)	
	Abdominal pain upper			1 (14.3%)
	Alcoholic pancreatitis		1 (5.9%)	
	Oesophageal varices haemorrhage		1 (5.9%)	
	Pancreatitis acute		1 (5.9%)	
General disorders and administration site conditions			1 (5.9%)	1 (14.3%)
	General physical health deterioration		1 (5.9%)	1 (14.3%)
Infections and infestations			2 (11.8%)	
	COVID-19		1 (5.9%)	
	Pneumonia aspiration		1 (5.9%)	
Nervous system disorders			1 (5.9%)	1 (14.3%)
	Coma		1 (5.9%)	
	Idiopathic generalised epilepsy			1 (14.3%)
Respiratory, thoracic and mediastinal disorders		1 (33.3%)		1 (14.3%)
	Acute respiratory failure	1 (33.3%)		
	Obstructive sleep apnoea syndrome			1 (14.3%)
Cardiac disorders			1 (5.9%)	

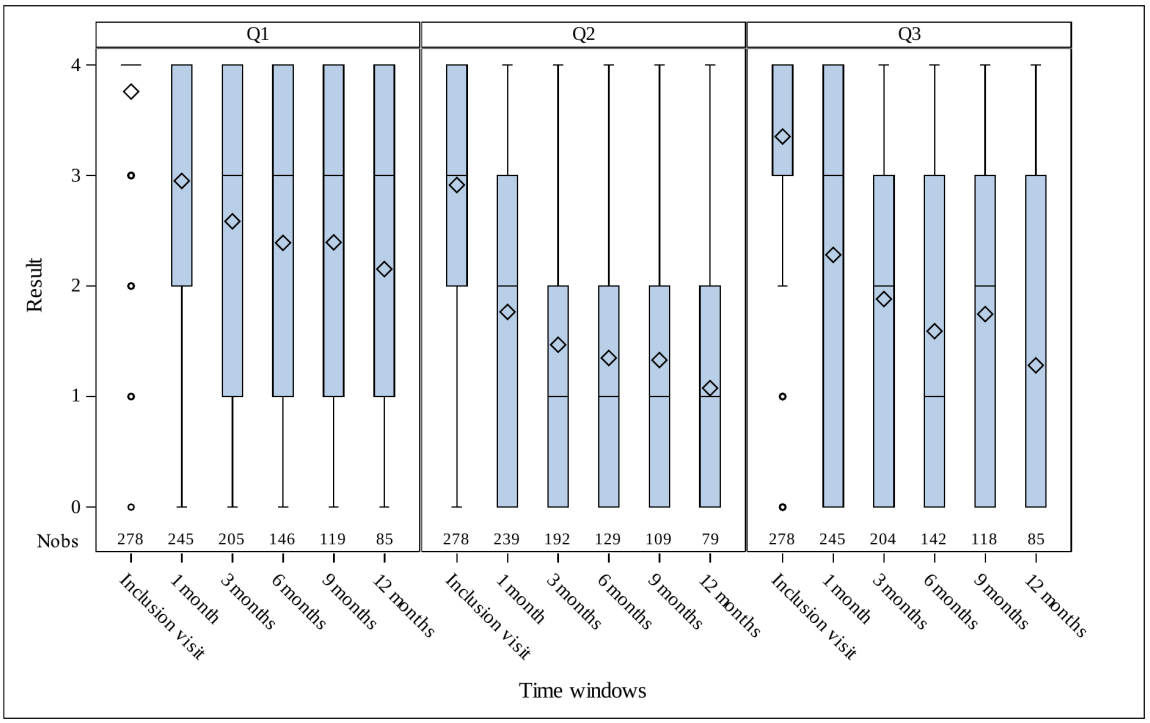
		<30 N = 52	[30-80[N = 173	[80-180[N = 44
	Atrial fibrillation		1 (5.9%)	
	Cardiac flutter		1 (5.9%)	
	Supraventricular tachycardia		1 (5.9%)	
Eye disorders			1 (5.9%)	
	Glaucoma		1 (5.9%)	
Metabolism and nutrition disorders			1 (5.9%)	
	Diabetes mellitus		1 (5.9%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			1 (5.9%)	
	Neoplasm malignant		1 (5.9%)	
Renal and urinary disorders			1 (5.9%)	
	Acute kidney injury		1 (5.9%)	
Surgical and medical procedures			1 (5.9%)	
	Alcohol detoxification		1 (5.9%)	

Results are presented as n (%). Patients are counted only once per primary SOC and PT. Range dose of baclofen: mean dose of baclofen since the first intake. Mean dose of baclofen was missing for 9 patients [1 with SAEs].

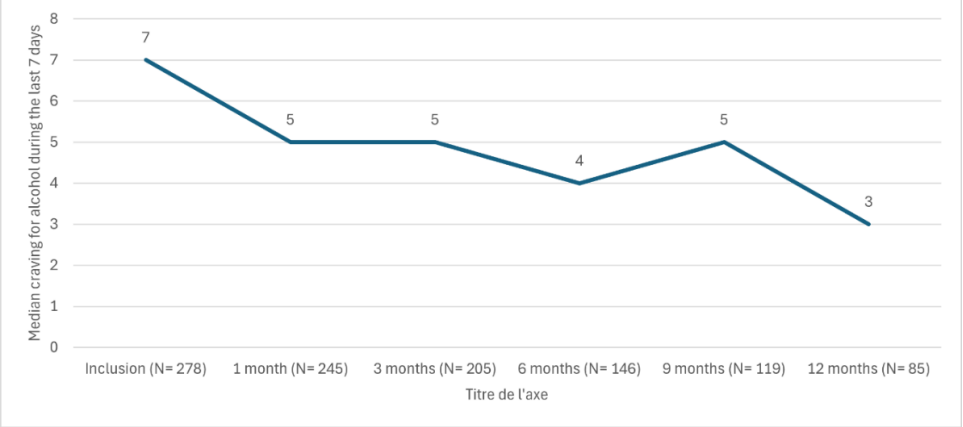
Supplementary Figures



Supplementary Figure 1. Clinical global impression of severity (CGI-S) throughout the study period. Results are presented in %.



Supplementary Figure 2. AUDIT-C questionnaire throughout the study period (Safety population, N= 278). Nobs, number of patients per visit. Q1: Frequency of drinks containing alcohol: Never [0] / Monthly or less [1] / 2-4 times a month [2] / 2-3 times a week [3] / 4 or more times a week [4]. Q2: Number of standard drinks containing alcohol on an ordinary day: 1 or 2 [0] / 3 or 4 [1] / 5 or 6 [2] / 7 to 9 [3] / 10 or more [4]. Q3: Frequency of six or more drinks during the same occasion: Never [0] / Less than monthly [1] / Monthly [2] / Weekly [3] / Daily or almost daily [4].



Supplementary Figure 3. Median score of craving for alcohol during the last 7 days.