BACLOVILLE

CLINICAL EFFICACY STUDY OF HIGH DOSE BACLOFEN IN REDUCING ALCOHOL CONSUMPTION IN HIGH RISK DRINKERS

(ClinicalTrials.gov Identifier: NCT01604330)

Coordinating investigator: P.JAURY (Department of General Medicine/ Paris Descartes)

***Scientific Committee*: J.R.Le Gall, A.Benyamina, R. de Beaurepaire, H.Falcoff. S.Sidorkiewicz.**
***Independent Data Safety Monitoring Board*: N.Simon, J.B.Trabut, L.Moachon.**
***Chief Scientist*: C.Le Jeunne.**
***Methodologists:* R.Porcher, L.Rigal, E.Perrodeau (J.Coste).**
***Clinical Research Unit Paris Centre*: J.M.Treluyer (Chief Project S.Poignant),**
***CRA:* A.Bruneau, A.Clabaux.**
***Pharmaceutical logistic* (AGEPS) Chief Project S.Manin.**
***Sponsor*: Assistance Publique-Hôpitaux de Paris (Chief Project Y.Vacher).**
***Funding*: French Ministry of Health and JPM (private donation).**

DECLARATION OF INTERESTS

Bouchara-Recordati/Ethypharm/
Novartis/Polpharma/Sanofi

BACLOVILLE

- Bacloville is a multicentric (60 centers) nationwide, pragmatic, therapeutic, randomized, double-blind trial **in primary care** assessing the efficacy and safety of high dose baclofen versus placebo **during 1 year**.
- With institutional sponsor.
- Bacloville was designed as a pragmatic risk reduction study.
- The study began in May 2012 and the last participant (320) was included in June 2013.
- The primary completion date was September 2014 (final data collection date for primary outcome measure).
- Data base was locked in October 2015.
- Here are presented preliminary results : some baseline patients characteristics , the flow chart **and the primary outcome**.
- Secondary efficacy outcomes, safety and tolerance are not available.

OBJECTIVES (1)

PRIMARY:

- effectiveness of one year treatment of baclofen compared to placebo on the reduction of alcohol consumption.
- The primary endpoint is the percentage of patients in each group with a low risk alcohol consumption or abstinent 12 months after treatment initiation,
- according to the patient-reported alcohol consumption (diary).
- A low risk alcohol consumption being (according to the WHO) a MDC (Mean Daily Consumption) between 1 and 20 g for women and between 1 and 40 g for men.

OBJECTIVES (2)

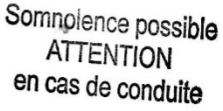
SECONDARY :

- Total alcohol consumption during the 12th month.
- Average monthly alcohol consumption.
- Numbers of abstinence and heavy drinking days.
- Craving : Visual Analogic Scale and OCDS Scale .
- SF-36, HAD (anxiety).
- DSM-IV for alcohol dependence.
- Laboratory variables.
- Alcohol consumption evaluated by the physician during the 12th month.
- Characterization of the population responding to baclofen.
- Determination of the optimal dose of baclofen.

OBJECTIVES (3)

SAFETY AND TOLERANCE:

- Adverse events (MedDRA classification).
- Biological tolerance.
- HAD (depression).



INCLUSION CRITERIA

- Adult patient (18-65) with an alcohol use disorder (high risk alcohol consumption (WHO) during the past three months: at least two times per month).
- Volunteer to participate in the trial and having given his written informed consent.
- Patient having no treatment for maintenance of abstinence (acamprosate,naltrexone) or prevention of relapse (disulfiram) for at least 15 days before the beginning of the trial.
- Patient informed about the possibility of drowsiness due to the treatment, the associated risks to drive vehicles (motorized or not) or use machines (including domestic use or recreation) and the execution of tasks requiring attention and precision.

NON INCLUSION CRITERIA

- Patient taking already baclofen or having taken baclofen.
- Patient pregnant, lactating, or of childbearing potential in the absence of effective contraception.
- Patient with severe psychiatric pathology (psychosis, including schizophrenia and bipolar disorders) that could compromise the observance.
- Patient with organic disease serious enough to forbid inclusion in the study according to the opinion of the investigator.
- Patient homeless.
- Patient without health insurance.
- Patient unable to properly fill the patient diary, and/or who cannot commit to one year of follow-up.

THERAPEUTIC SCHEDULE

- The drug was administered orally for a maximum of **52** consecutive weeks.
- For the first 3 days, patients received the drug in a dose of 5 milligrams three times a day (it could be four or five times a day); then the dose was increased to a maximum of **300** milligrams a day.
- Titration duration was flexible.
- It was not asked to stop drinking.
- In case of intolerance, dosage could be decreased.

FLOW CHART

Enrollment

327 Assessed for eligibility

7 Excluded

320 Randomized

Allocation

162 Allocated to **baclofen**

158 Allocated to **placebo**

49 withdrew prematurely from the study including 7 deaths (5 due to alcohol) and 23 lost to follow-up

Follow-Up

53 withdrew prematurely from the study including 3 deaths (1 due to alcohol) and 28 lost to follow-up

113 followed-up for 12 months

105 followed-up for 12 months

Some characteristics of the patients

- *Average age* = 48 years old (23-65)(48 in both arms).
- *Male* = 70%. (baclofen 71%/placebo 69%).
- *Mean daily alcohol intake*:
- 12,8 alcohol unit/day (baclofen group).
- 12,9 alcohol unit/day (placebo group).
- *Cannabis* (regularly) : 27 patients.
- *Cocaïne* (regularly): 4 patients.
- *Heroin* (regularly) : 2 patients.
- *Buprenorphine* : 20 patients (11/9).
- *Methadone* : 17 patients (11/6).
- *Behavioural addictions* :23 patients.

characteristics of the patients trajectories

- **Exposure to family history or trauma – %**
  - Alcohol problems in the family 61.9%
  - Trauma in childhood or adolescence 31.8%
- **Trajectories of alcohol use**
  - Age of drinking onset –median (IQR) 16.0 (14.0 – 18.0)
  - Age of first intoxication – median (IQR) 17.0 (15.0 – 20.0)
  - Age of regular drinking – median (IQR) 25.0 (20.0 – 35.0)
  - Age of loss of control – median (IQR) 35.0 (27.0 – 41.0)
  - Age of awareness – median (IQR) 37.0 (30.0 – 45.0)

Main analysis of the primary outcome

- The primary endpoint is the Mean Daily Consumption (MDC) during the 12th month with success defined as abstinence or a low level of consumption.
- Analysis is done in ITT (Intent To Treat).
- Patients receiving marketed baclofen during the study follow-up are considered as failures.
- Patients deceased during the study are considered failures if their deaths can be attributed to alcohol or the study.
- In the case of missing information about patient consumption, data are imputed.

Proportion of successes in the two groups with multiple imputation.

- Comparisons of baclofen vs placebo taking into account the intra-class correlation, 95% CI = 95% confidence interval.

	Baclofen (162)	Placebo (158)	Absolute difference (95% CI)	Risk ratios (95% CI)
Imputed data	**56.8%**	**36.5%**	**20.3%** (7.3 ; 33.3)	1.56 (1.15 ; 2.11)

- Wald test for the estimated combined risk ratio yields **P = 0.004**.
- 3 sensitivity analyses corroborate this conclusion.

THANKS FOR YOUR LISTENING

- And many thanks to all the patients, the General Practitioners and other investigators who participate to Bacloville.
- To the SFTG.
- Not to forget AUBES and JPM. (+RESAB/Baclofene Association/ Olivier Ameisen Association)
- **And of course Pr Olivier Ameisen†.**

		Baclofene		Placebo	RR [95% CI]
	N	% success	N	% success	
Complete cases	61	39.3	78	15.4	2.56 [1.28; 5.12]
Sensitivity 1	162	24.8	158	9.9	2.49 [1.44; 4.31]
Sensitivity 2	162	27.7	158	12.2	2.28 [1.42; 3.66]
Primary analysis	**162**	**56.8**	**158**	**36.5**	**1.56 [1.15; 2.11]**