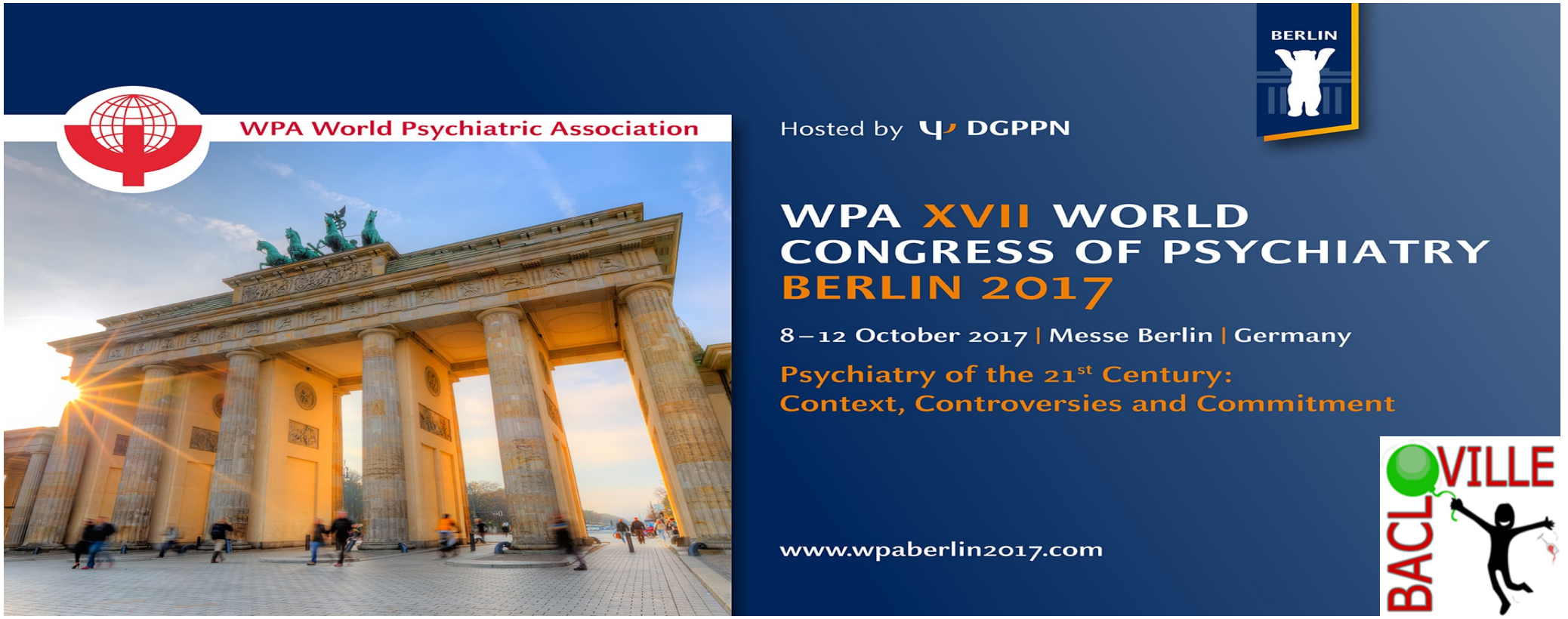

Pr Philippe Jaury* Paris Descartes University France

Dr Stéphanie Sidorkiewicz Paris Descartes University

*DECLARATION OF INTERESTS :

Bouchara-Recordati/Ethypharm/Novartis/Polpharma/Sanofi/Indivior

BACLOVILLE

Alcohol Treatment: Pragmatic Therapeutic Trial Randomized, Double-blind for a Year in Ambulatory Care of Baclofen Versus Placebo.

(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).**

BACLOVILLE

- Bacloville is a multicentric (60 center 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.

OBJECTIVES

PRIMARY:

- effectiveness of one year treatment of baclofen compared to placebo on the reduction of alcohol consumption.
- The primary endpoint (ITT) is the percentage of patients in each group with a low risk alcohol consumption (WHO) or abstinent 12 months after treatment initiation,
- According to the patient-reported alcohol consumption (diary).

INCLUSION CRITERIA

- All 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).
- Patient with severe psychiatric pathology (psychosis, including schizophrenia and bipolar disorders) could be included according to the opinion of the investigator.
- Patient with organic disease could be also included according to the opinion of the investigator.

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 could be 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.

Statistical Analysis Plan

- <u>Statistical methods:</u>

- Missing data managed with multiple imputation by chained equations « MICE ».
- Software R version 3.2.2.

- <u>Validated by 3 independants experts :</u>

- Pr Bruno Falissard, Paris Sud University.
- Pr Gilles Chatellier, Paris Descartes University.
- Pr Katie Witkiewitz, Dpt of Psychology, New Mexico University.

FLOW CHART

Enrollment

327 Assessed for eligibility

7 Excluded

320 Randomized

Allocation

162 Allocated to **baclofen**

158 Allocated to **placebo**

Follow-Up

49 withdrew prematurely from the study including 7 deaths (5 due to alcohol) and **23** lost to 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
Analysed = 162

105 followed-up for 12 months
Analysed = 158

Some baseline patients characteristics

Variable	Baclofen (n=162)	Placebo (n=158)
Median age (IQR) — yr	46 (40-54)	47 (40-55)
Men, no. (%)	115 (71)	109 (69)
Mean daily alcohol consumption	128 g	129 g
Bipolar disorder, no. (%)	13 (8)	9 (6)
Suicide attempts, no. (%)	37 (23)	30 (19)
Regular consumption of cannabis, no. (%)	17 (11)	10 (7)
Regular consumption of cocaine, no. (%)	1 (1)	2 (1)
Regular consumption of heroin, no. (%)	2 (1)	0 (0)
Buprenorphine, no. (%)	9 (6)	9 (6)
Methadone, no. (%)	11 (7)	6 (4)

doses

Doses (mg/d)	Baclofen	Placebo
Median	180	210
Q1; Q3	100; 270	138; 290
Min; max	15; 420	15; 300

Primary endpoint : Proportion of successes in the two groups with multiple imputation.

	Baclofen (162)	Placebo (158)	Absolute difference (95% CI)	Risk ratios (95% CI)
Imputed data	57%	36%	21% (8.1 ; 33.8)	1.59 (1.17 ; 2.15)

- Wald test for the estimated combined risk ratio yields ***p* = 0.003**.
- The complete-cases population analysis,
- and the two sensitivity analyses confirmed these results.

Safety and tolerance (1)

- More adverse events (AE) occurred in patients who received baclofen (86%) than in patients under placebo (80%) but it was not significant.
- The three most frequent adverse events in decreasing order were:

  - drowsiness (reported by 56% patients in the baclofen arm and 42% in the placebo arm),

  - fatigue,

  - and insomnia.
- the difference was significant only for drowsiness, fatigue, vertigo, paresthesia and tinnitus.

Safety and tolerance (2)

- Serious adverse events (SAE) occurred more frequently in the baclofen than placebo arm (85 [38%] vs 36 [23%] patients; *p*=0.02).
- and were more often possibly related to the treatment according to the investigators (19%/7%)(*p*= 0.002).
- Seven patients died in the baclofen arm (including one suicide and one death which occurred before treatment initiation),
- and three in the placebo arm.
- No death was classified both by investigators and by an independent committee as potentially related to study treatment.

CONCLUSIONS

- The primary endpoint is positive in favour of the baclofen.
- There are more adverse events and serious adverse events with the baclofen but they are expected and well known.
- High-dose baclofen could be a useful medication for outpatients who want to achieve low-risk alcohol consumption , without prior withdrawal.
- Doctors need to be trained and patients need to take their treatment properly.

THANK YOU 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†.**

Sensitivity Analysis

	Baclofen		Placebo		RR (95% CI)
	N	% Success	N	% Success	
Complete cases	61	39.3	79	15.2	2.59 (1.29 to 5.19)
Sensitivity 1	162	24.8	158	9.9	2.49 (1.44 to 4.31)
Sensitivity 2	162	27.7	158	12.2	2.28 (1.42 to 3.66)
Primary analysis	162	56.8	158	35.8	1.59 (1.17 to 2.15)