ACTUALITES THERAPEUTIQUES
Baclofene

Pr Michel REYNAUD

Président du Fonds Actions Addictions

addictaide.fr

CONFLICT OF INTEREST

- Ethypharm : PI for Alpadir study
- Lundbeck : Member of scientific board
- DA Pharma : Member of scientific board
- Indivior : Member of scientific board

BACLOFEN: CLINICAL EVIDENCE - RCTs

Study	N	Duration	Condition	Daily dose	Efficacy	Safety
Addolorato et al., 2002	39	4 weeks	AUD	30 mg	•Proportion of abstinent patients ↑ •Cumulative abstinence duration ↑	No diff.
Addolorato et al., 2007	84	12 weeks	AUD & liver cirrhosis	30 mg	•Proportion of abstinent patients ↑ •Cumulative abstinence duration ↑	No diff.
Garbutt et al., 2010	80	12 weeks	AUD	30 mg	•No difference in: %HDD & %ABS	No diff.
Addolorato et al., 2011	42	12 weeks	AUD	30 mg/ 60 mg	•No difference in: HDD & abstinent days Post hoc: Number of drinks/day ↓	No diff.
Leggio et al., 2012 (Post hoc analysis of the study by Addolorato et al., 2007)	24	12 weeks	AUD + Hep. C + liver cirrhosis	30 mg	•Proportion of abstinent patients ↑	No diff.

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BACLAD STUDY

European Neuropsychopharmacology (2015) 25, 1167-1177

ELSEVIER

www.elsevier.com/locate/euroneuro

High-dose baclofen for the treatment of alcohol dependence (BACLAD study): A randomized, placebo-controlled trial

Christian A. Müller[a,*], Olga Geisel[a], Patricia Pelz[a], Verena Higl[a], Josephine Krüger[a], Anna Stickel[a], Anne Beck[a], Klaus-Dieter Wernecke[b], Rainer Hellweg[a], Andreas Heinz[a]

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[b]*Charité - Universitätsmedizin Berlin and Sostana GmbH Berlin, Germany*

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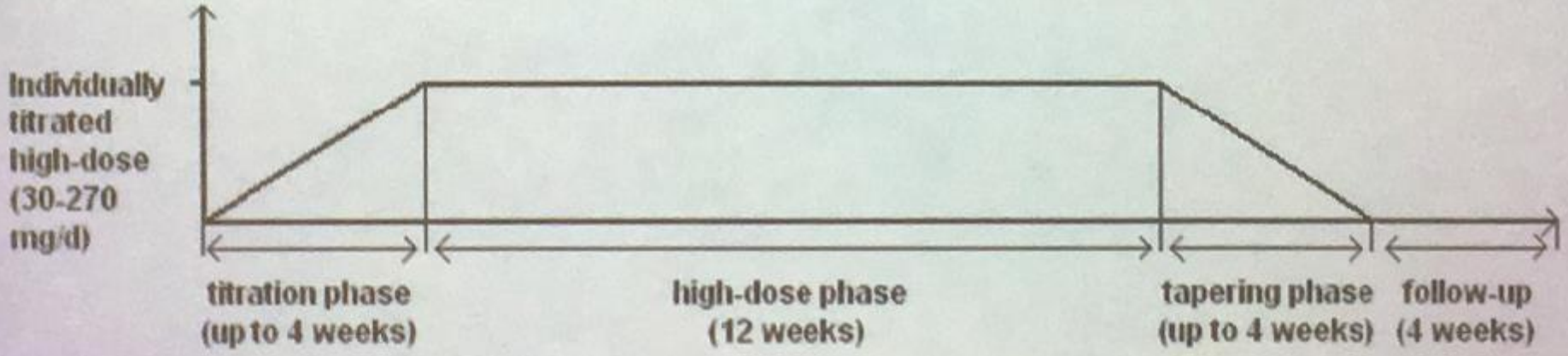
TRIAL PROFILE



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KEY INCLUSION / EXCLUSION CRITERIA

INCLUSION CRITERIA

- Women & men: age of ≥ 18 and < 65 years
- Diagnosis of alcohol dependence (ICD-10 & DSM-IV-TR)
- Alcohol consumption of at least 2 HDD per week + an overall alcohol intake of 21/14 drinks per week (men/women)
- Completed detoxification before randomization
- Last alcohol consumption within 7 to 21 days

EXCLUSION CRITERIA

- Significant internal, psychiatric (axis I diagnoses other than alcohol or nicotine dependence) or neurological conditions
- Current treatment with psychotropic drugs that could affect study outcome
- Epileptiform convulsions

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OUTCOME MEASURES

Primary outcome measures:

- Total abstinence during high-dose phase
- Cumulative abstinence duration during high-dose phase

Secondary outcome measures:

- Safety and tolerability of the study drug
- Drop-out rate
- Changes in psychiatric assessments compared to baseline

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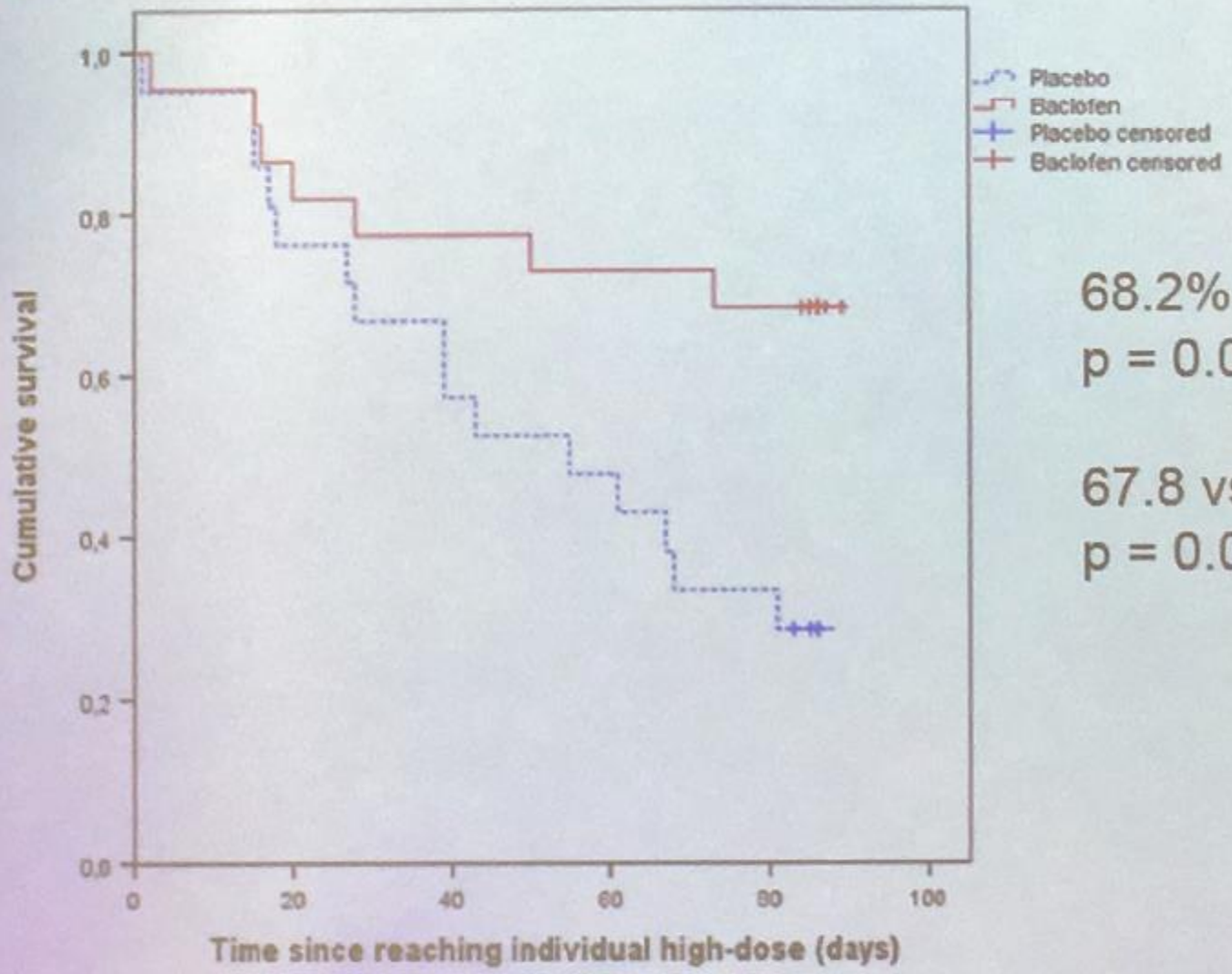
HIGH-DOSE PHASE

a



68.2% vs. 23.8%
p = 0.014

67.8 vs. 51.8 days
p = 0.047

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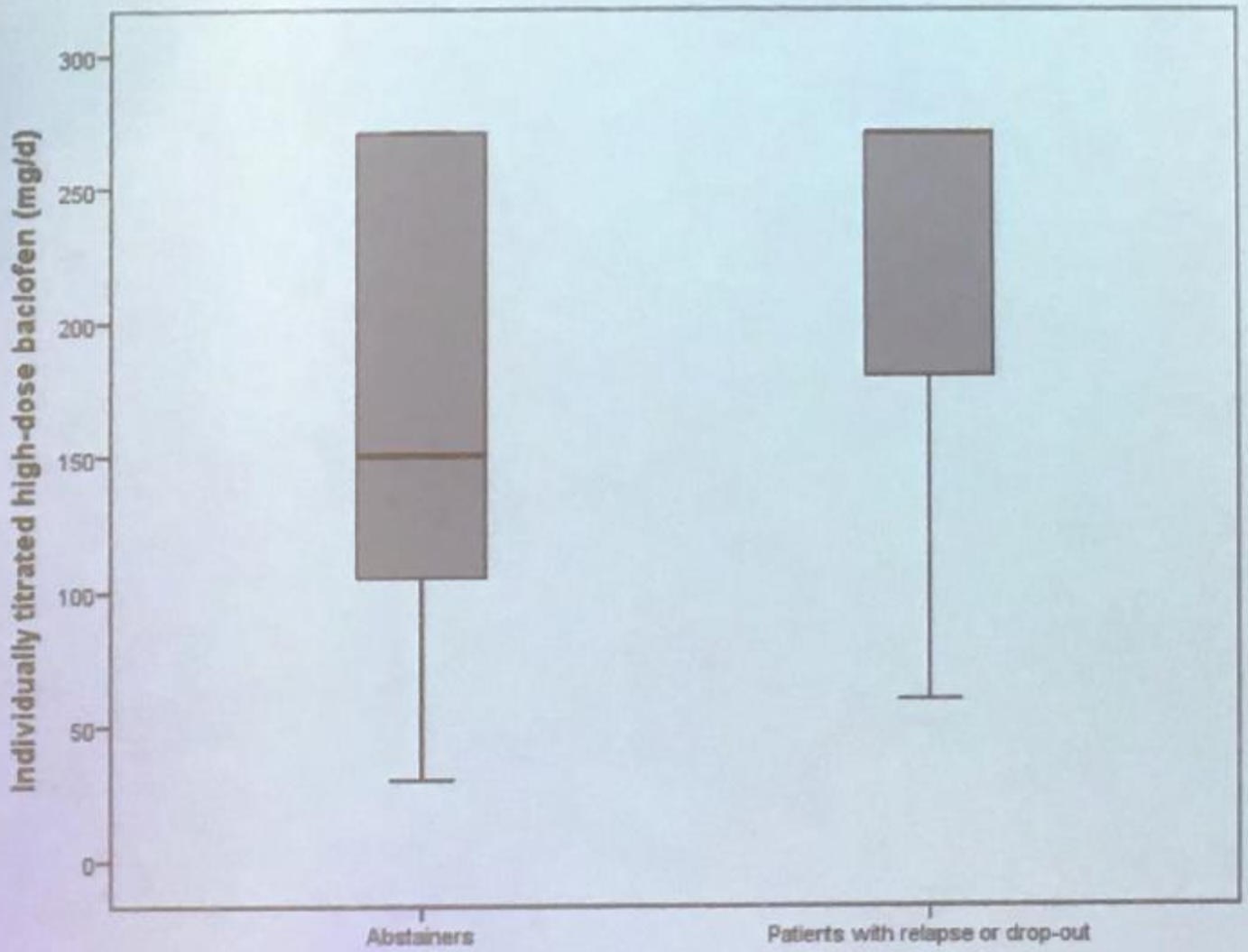
DOSE-RESPONSE EFFECT?



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SUMMARY

- Individually titrated high-dose baclofen supported alcohol-dependent patients effectively in maintaining alcohol abstinence
- Baclofen showed a high tolerability
- No evidence for abuse liability
- Efficacy does probably not depend on a clear cut-off dose
- Dosing needs to be conducted individually including close monitoring

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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).

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)

BACLOVILLE

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.

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.

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.

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.

European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

ELSEVIER

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Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: A multicentre, randomised, double-blind controlled trial

Esther M. Beraha[a], Elske Salemink[a,1], Anna E. Goudriaan[b,c,d,1], Abraham Bakker[h], David de Jong[a], Natasha Smits[e], Jan Willem Zwart[e], Dick van Geest[f], Pieter Bodewits[g], Tom Schiphof[f], Harma Defourny[e], Mirjam van Tricht[b], Wim van den Brink[b,c,2], Reinout W. Wiers[a,*,2]

[a]*Addiction Development and Psychopathology (ADAPT) Laboratory, Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands*
[b]*Academical Medical Centre (AMC), Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands*
[c]*Amsterdam Institute for Addiction Research, Department of Psychiatry, University of Amsterdam, Amsterdam, The Netherlands*
[d]*Arkin Institute for Mental Health Care, Amsterdam, The Netherlands*

Study design

- Multicentre trial in two inpatient treatment centres (SolutionS Center & U-Center) and three outpatient treatment centres (The Home Clinic, Ready for Change, and Terwille) in the Netherlands
- N = 151 patients with AD
- 3 groups: high-dose baclofen (N= 58; up to 150 mg), low-dose baclofen (N= 31; 30 mg), and placebo (N=62)
- Duration: 16 weeks
- 6 weeks titration, 10 weeks high-dose phase

Exclusion criteria

- Current severe axis I disorder (besides anxiety, depression, or bipolar disorder)
- Any primary diagnosis of substance dependence other than alcohol
- Severe physical illness or pregnancy
- Anti-hypertensive medication
- Current or recent pharmacological treatment for AD (acamprosate, naltrexone, disulfiram,…..)
- Use of baclofen in the past 30 days

Medication & Titration

- Identical 10 mg tablets
- Three times a day
- Dose was increased with 30 mg/week (with physician consult)
- High-dose group: up to 150 mg/day within 6 weeks
- Low-dose group: 30 mg/day
- Double blind

Psychosocial treatment

- In-patients: 4 or 6 weeks inpatient treatment programme (Minnesota Model, CBT) followed by weekly outpatient groupsessions
- Out-patients: at least one weekly group- or individual therapy session

Procedure

- screening
- 3 testsession: 0, 4, and 16 weeks
- 6 weekly visits with a physician during titration phase (6 weeks)
- 5 bi-weekly visits with a psychologist during the high-dose phase (10 weeks)
- After 16 weeks patients were deblinded from the independent physician

Outcome measures

- **Primary outcome measure:**
  - Time to first relapse

- **Secundary outcome measures:**
  - Proportion of patients relapsed
  - Proportion of patients continously abstinent
  - Safety and tolerability
  - Changes in craving, anxiety, and depression
  - Dose-response effect

Results

- Patient's characteristics

	Total (N= 151)	High-dose baclofen (N=58)	Low-dose baclofen (N=31)	Placebo (N= 62)
Demographics				
Age (years)	44.8 (9.6)	45.8 (9.2)	44.7 (11.3)	44.0 (9.2)
Men	104 (68.9%)	41 (70.7%)	20 (64.5%)	43 (69.4%)
Married	82 (54.3%)	36 (62.1%)	17 (54.9%)	29 (46.8%)
Employed	88 (58.3%)	37 (63.8%)	18 (58.1%)	33 (53.2%)
Alcohol use				
Alcohol (gr/day)	141.8 (84.8)	147.0 (84.9)	132.5 (85.2)	141.7 (85.5)
Days abstinent	11.8 (4.4)	11.9 (4.7)	11.9 (4.3)	11.8 (4.3)
Duration of alcohol abuse (years)	19.5 (11.5)	18.8 (10.7)	21.5 (13.1)	19.0 (11.5)
Number of previous detoxifications	1.6 (2.8)	1.1 (1.6)	1.8 (2.9)	2.0 (3.6)

Discussion

- Contrary results to first RCT (Müller et al., 2015)
- Differences:

1) Doses
2) Treatment setting and psychosocial support
3) Patient population

1) Doses

- Max. dose of 150 mg and mean dose of 94 mg/day vs. max. 270 mg and mean dose of 180 mg (Müller et al., 2015)
- Dose-response effect
- BUT:
  - No dose-response effect in Müller et al., 2015
  - Positive outcomes with low doses (30-60 mg; Addolorato et al., 2001;2007; Carter et al., 2009)

2) Psychosocial support

- Majority (119 out of 151 patients) were inpatients for at least 28 days
- Extensive psychosocial treatment
  - Low doses
  - Large placebo effect

⟶ no additional effect to intensive inpatient treatment?

3) Patient population

- Difference in alcohol consumption:

140 gr/day vs. 200 gr/day (Müller et al.,2015)

→ Only effective in patients with higher drinking levels?

Conclusion

- No positive effect of high-dose or low–dose baclofen
- Indications for a dose response effect
- Only effective for heavy drinking AD patients with limited psychotherapy?

ALPADIR

A randomized, double blind, placebo- controlled efficacy study of high-dose baclofen in alcohol dependent patients

Pr Michel REYNAUD
Hôpital Paul Brousse
Département de Psychiatrie et d'Addictologie

UNIVERSITÉ PARIS SUD
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PROTOCOL

Primary objective

To assess the efficacy of high dose baclofen (180mg) compared to placebo on **continuous abstinence rate during 20 weeks** (after detoxification and in association with Brenda therapy sessions)

PROTOCOL

MAIN INCLUSION CRITERIA

Alcohol dependent patients (DSM IV criteria)

Detoxification 3-14 days before randomization

At least one previous abstinence attempt

MAIN EXCLUSION CRITERIA

Need for a stay after detoxification in a healthcare and rehabilitation institution

Need for a heavy psychosocial follow up

Epilepsy or history of epilepsy

Suicidal risk or history of suicide

Concomitant treatment with psychotropic drugs, except antidepressants at stable dose for 2 months, diazepam and oxazepam

SAMPLE SIZE → 316 patients to be randomized

HYPOTHESIS **placebo response 25%**
baclofen response 45%

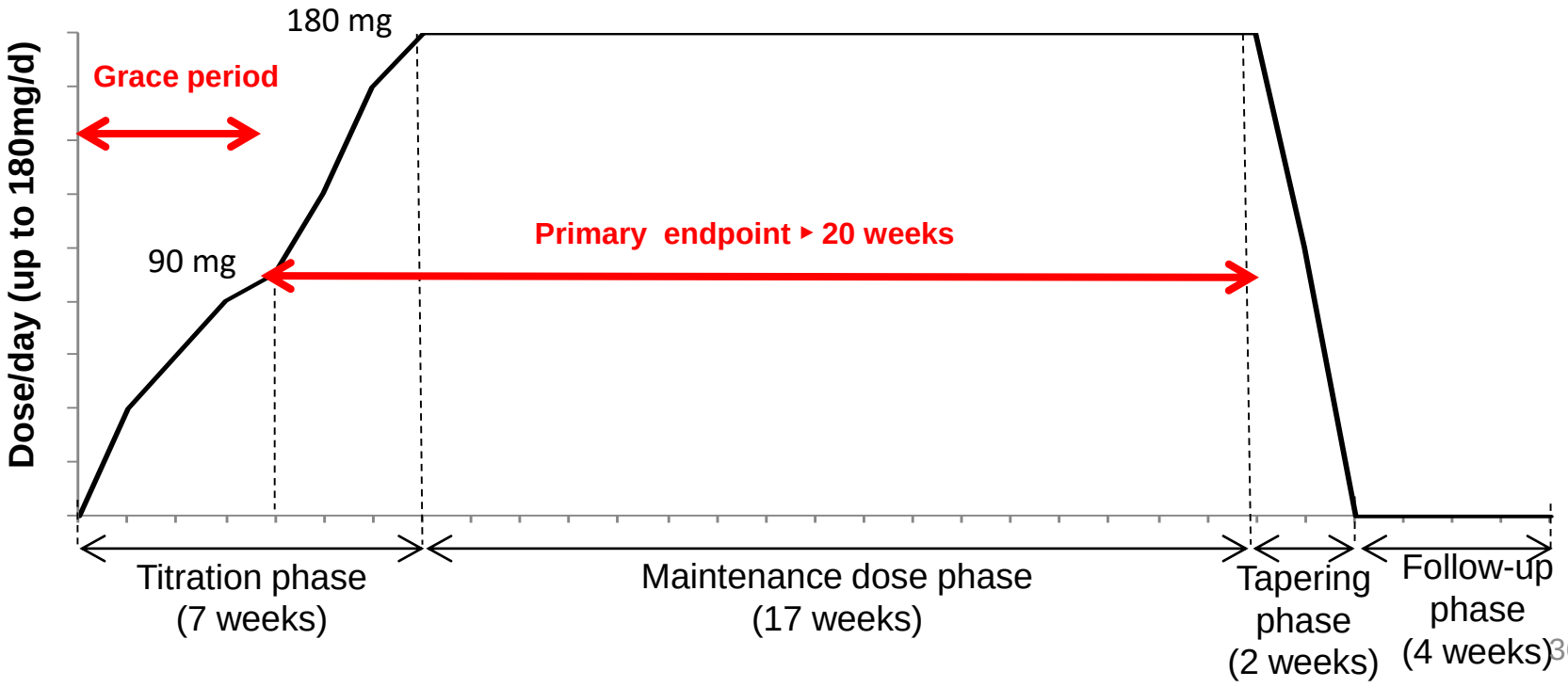
ENDPOINTS AND TREATMENT

PRIMARY ENDPOINT ► **Continuous abstinence rate during 20 weeks** of treatment from D29 to D168
(D1 to D28: grace period)

SECONDARY ENDPOINTS ►**Total alcohol consumption (TAC)** ► **Heavy drinking days (HDD)**
change from baseline (pre detoxification) to month 6

QUESTIONNAIRES AND SCALES: OCDS, HAD, CGI, AlQoL9, liver biomarkers

SAFETY: adverse events



POPULATIONS AND BASELINE CHARACTERISTCS

POPULATIONS

ITT 320 patients (randomized) ►158/162

SAF 316 patients (at least one dose of treatment) ►157/159

FAS 310 patients (SAF+one data post randomisation) ►**155/155**

PP 279 patients (no major protocol deviations) ►142/137

PREMATURE WITHDRAWALS **ITT population - % patients (n)**	**Baclofen** **N=158**	**Placebo** **N=162**	**Total** **N=320**
TOTAL	37.3% (59)	43.8% (71)	**40.6% (130)**
Withdrawal of consent	17	16	**33**
Lack of efficacy	6	**20**	26
Adverse event	10	**14**	24
Lost to follow up	14	6	20
Non compliance	6	8	14
Protocol deviation	5	7	12
Pregnancy	1	0	1
Before Day 29	5	9	14

DEMOGRAPHICS

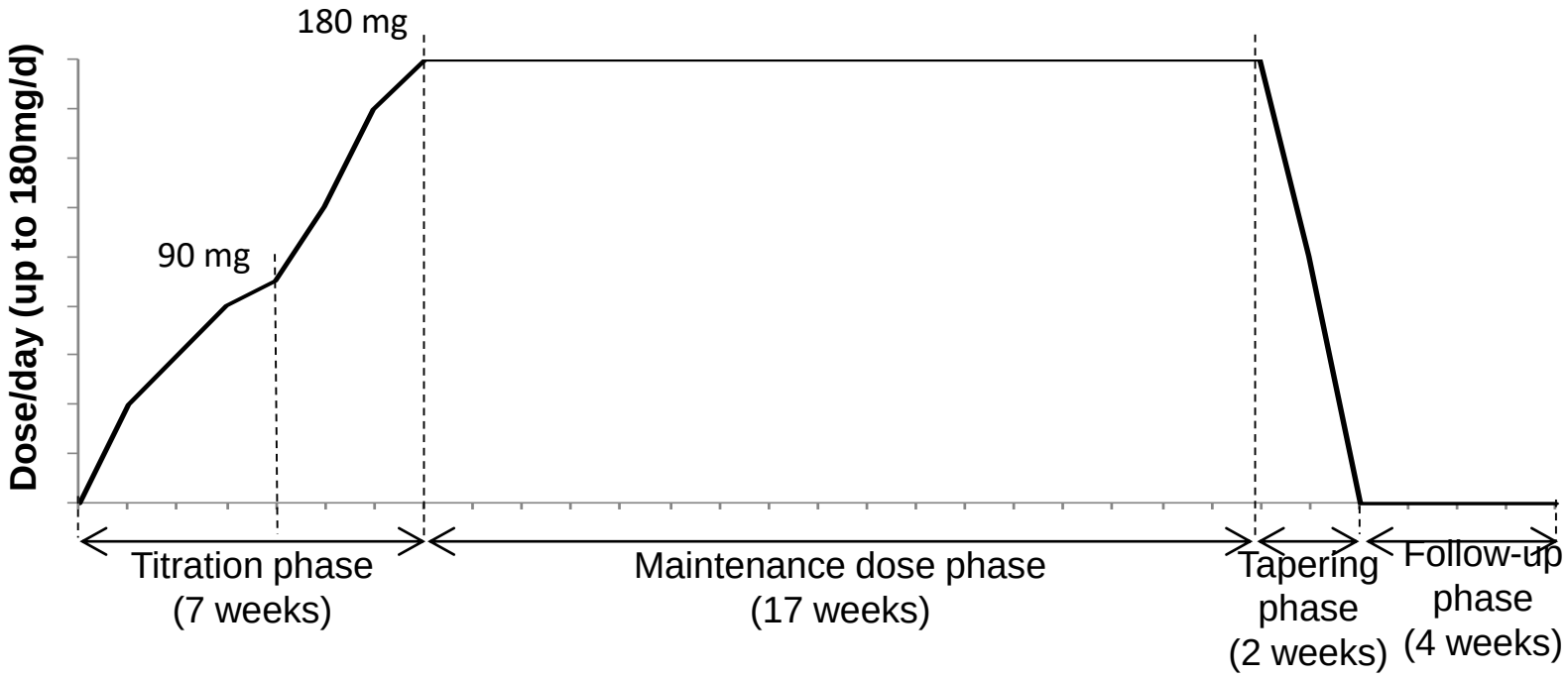
FAS population **Médian (min-max)**	**Baclofen** **N= 155**	**Placebo** **N= 155**
Age (years)	**48** (23- 79)	**50** (23- 75)
Sex ratio M/F (%)	76.1 / 23.9	69.0 / 31.0
Age of 1st alcohol consumption (years)	17 (6-45)	18 (5- 54)
Duration of alcohol dependence (years)	**10** (0- 43)	**13** (0 -45)
Duration of detoxification (days)	**7** (4-16)	**7** (3-15)

No significant difference between the 2 groups

BASELINE ALCOHOL CONSUMPTION (TLFB)

FAS population Mean ± SD	Baclofen N= 155	Placebo N= 155
Total alcohol consumption (g/d) TAC	**95.5 ± 75.6**	**93.6 ± 65.5**
✓ Male	104.0 ± 82.0	101.3 ± 67.1
✓ Female	68.2 ± 40.0	76.5 ± 59.0
Heavy drinking days /28 days HDD	**17.9 ± 10.2**	**17.6 ± 10.0**
Abstinent days/28 days	4.6 ± 6.7	5.1 ± 7.3
Drinking risk level (WHO) % patients		
✓ Low risk	13.5%	15.5%
✓ Medium risk	18.1%	14.2%
✓ High risk	29.7%	26.5%
✓ Very high risk	38.7%	43.9%
	68.4	**70.4**

POSOLOGY



SAF population	Baclofen N= 157	Placebo N= 159
Maintenance posology (mg/d) Mean ± SD	**153.5** ± 40.5	**172.5** ± 23.5
Patients having reached 180 mg or 9 tablets (%)	65.6%	88.8%
Posology at Day 28 (mg/d) Mean ± SD	86.2 ± 13.5	86.1 ± 14.1

EFFICACY RESULTS

Management of missing data (alcohol consumption)

Multiple imputation (MI)

Most plausible outcome (MPO)

Worst case (WC)

Main analysis ►FAS population and Multiple Imputation

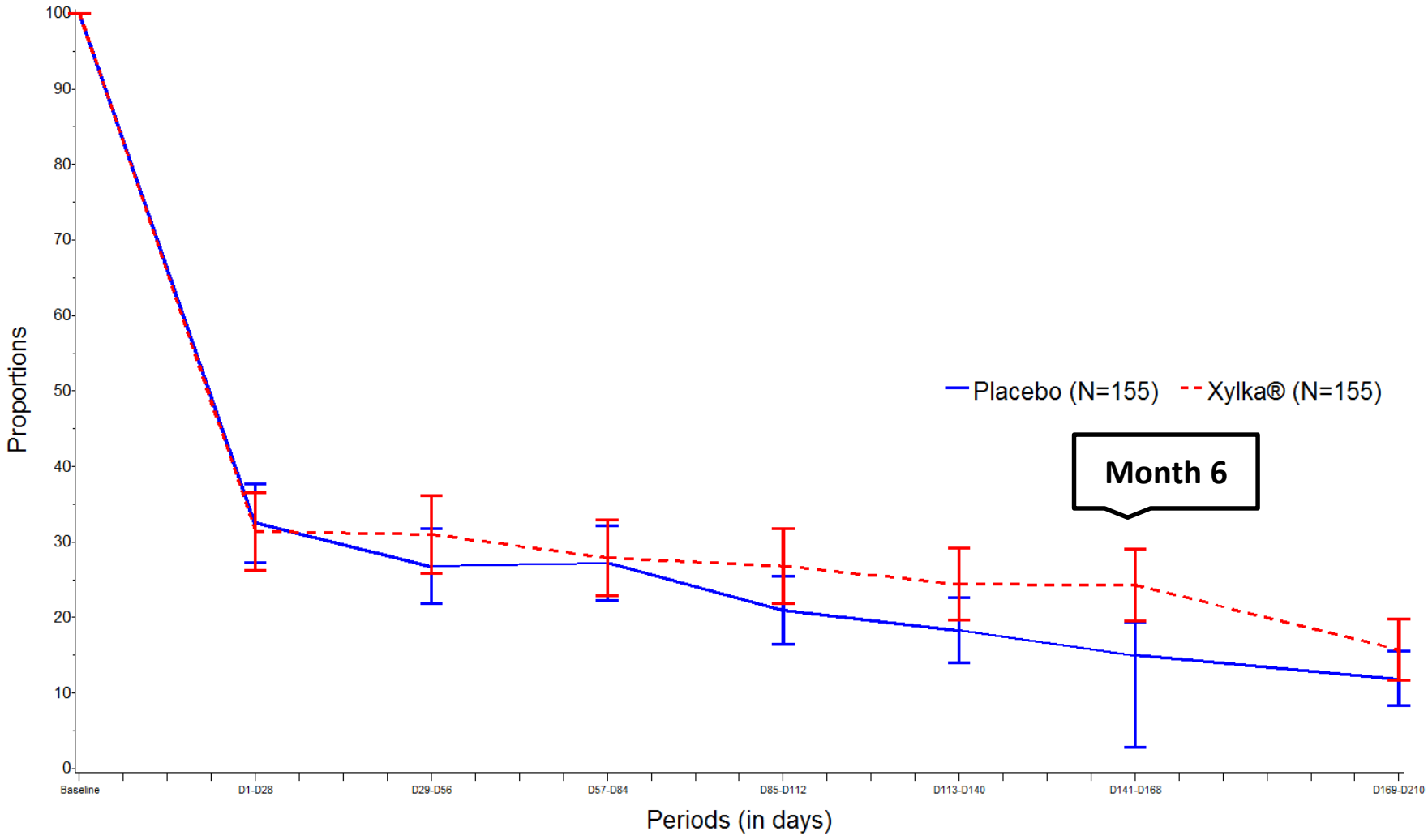
ABSTINENCE OVER 20 WEEKS

	Baclofen	Placebo	Difference to placebo[(1)]	
	% of patients [95%CI]	% of patients [95%CI]	Odds ratio [95%CI]	*p*
Main analysis FAS/MI	**11.9 %*** [8.3 ; 15.5]	**10.5 %*** [7.0 ; 13.9]	**1.20** [0.58 ; 2.50]	**0.619**
Sensitivity analyses				
FAS/MPO	**19.4 %** [13.1 ; 25.6]	**16.1 %** [10.3 ; 21.9]	1.33 [0.73 ; 2.44]	0.352
FAS/WC	**8.4 %** [4.0; 12.8]	**7.1 %** [3.1; 11.1]	1.26 [0.53 ; 2.95]	0.600
PP/MI	**13.0 %*** [9.2 ; 16.7]	**11.8 %*** [8.2 ; 15.4]	1.18 [0.57 ; 2.46]	0.657

[(1)]Logistic model with treatment group, drinking risk level at baseline and pooled centers as covariates

***Mean of the five imputed data sets**

ABSTINENT PATIENTS PER MONTH

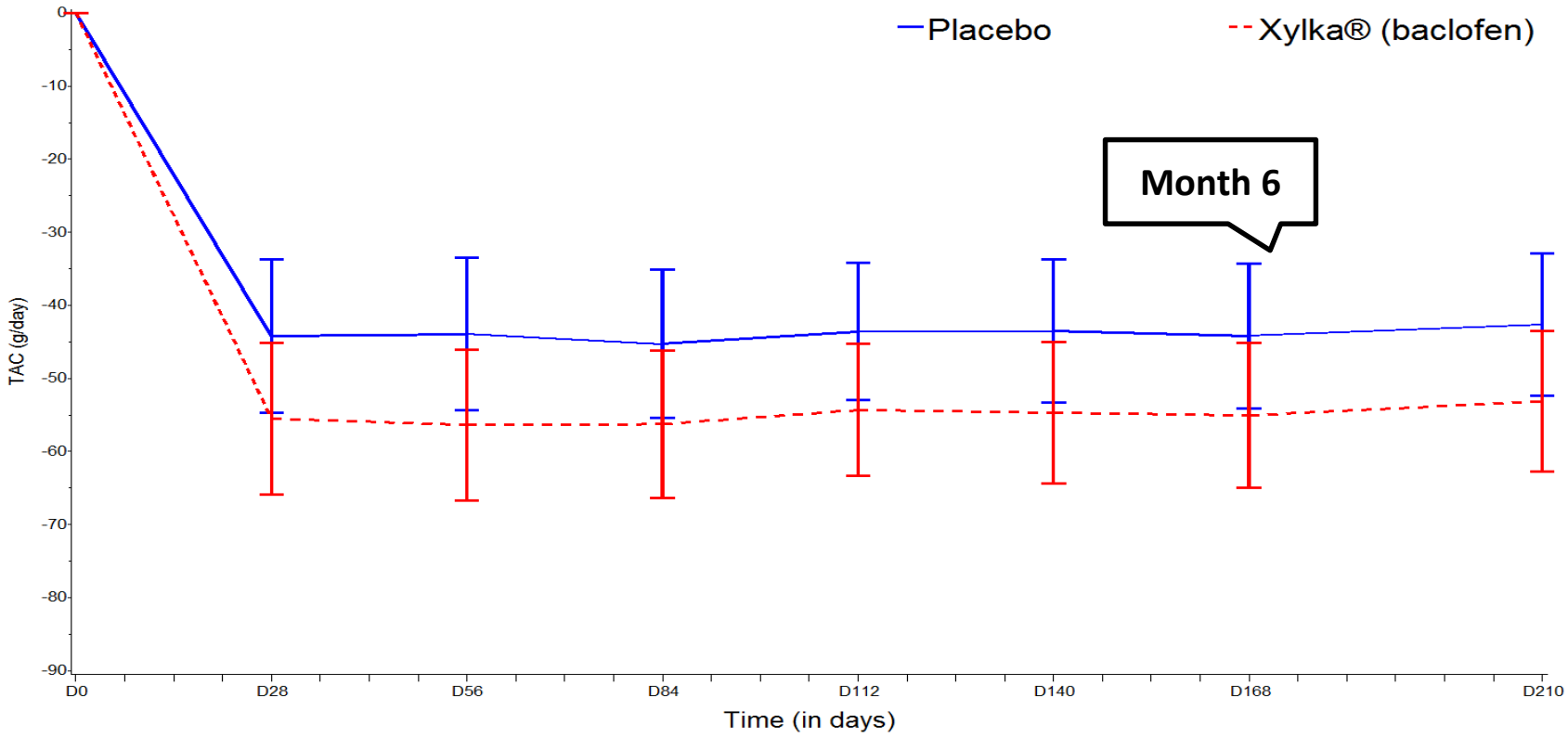


TAC - CHANGE FROM BASELINE

Adjusted change from baseline to month 6*

*calculated using generalized model with treatment group, drinking risk level at baseline and pooled centers as covariates

LSmeans [95%CI]	Baclofen	Placebo	Difference to placebo	*p*
TAC g/day	**-55.06** [-64.94;-45.19]	**-44.16** [-54.08;-34.25]	**-10.90** [-23.68;1.89]	**0.095**

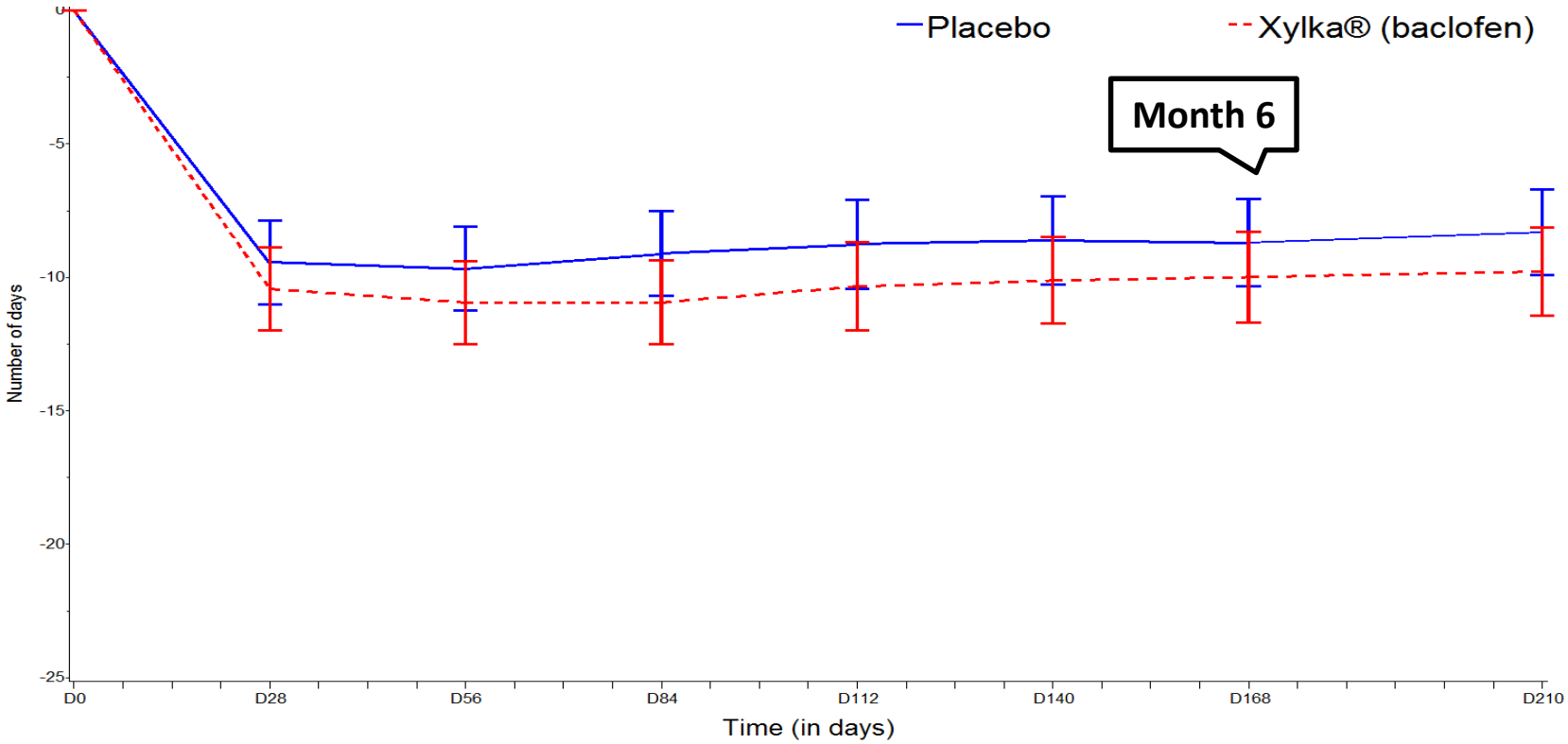


HDD - CHANGE FROM BASELINE

Adjusted change from baseline to month 6*

*calculated using generalized model with treatment group, drinking risk level at baseline and pooled centers as covariates

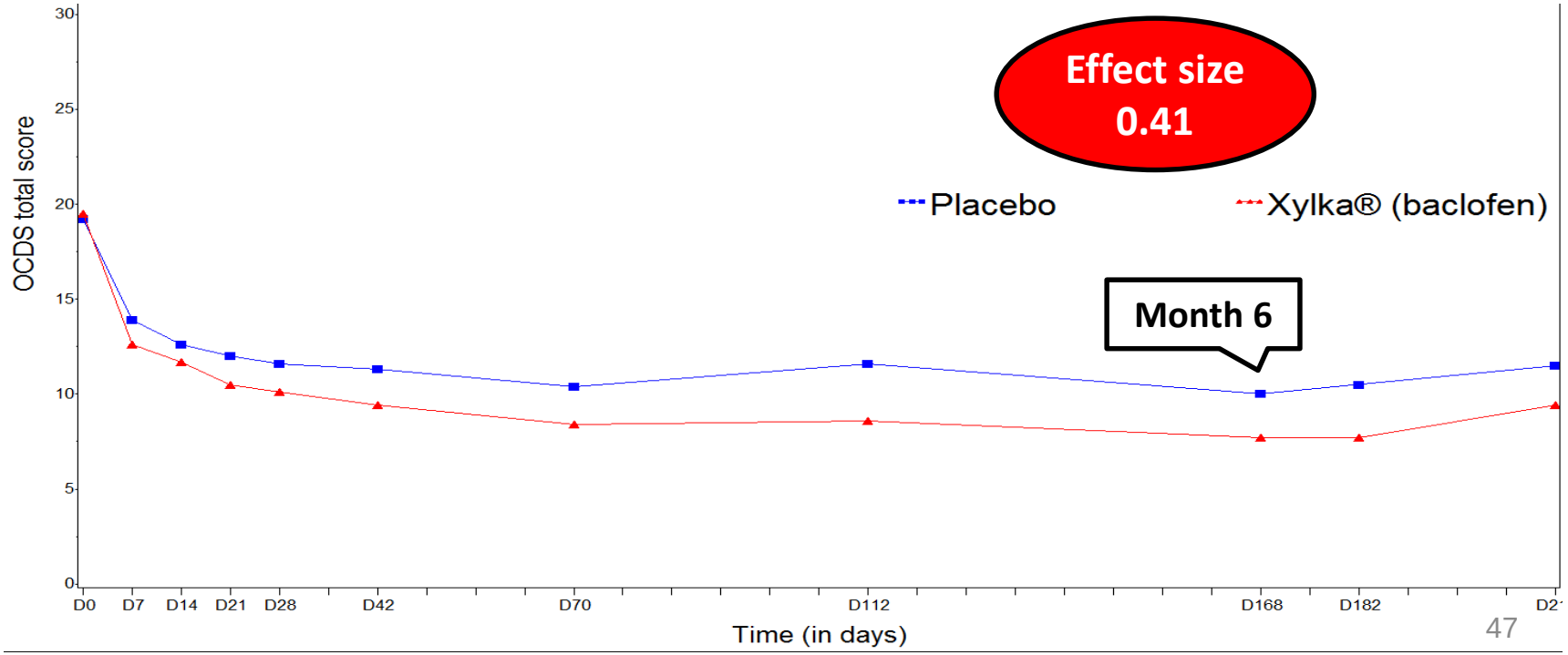
LSmeans [95%CI]	Baclofen	Placebo	Difference to placebo	*p*
HDD days/month	**-9.9** [-11.69;-8.29]	**-8.70** [-10.34;-7.07]	**-1.29** [-3.38;0.81]	**0.228**



OCDS – CHANGE AT MONTH 6

Total OCDS score (0-40)				
FAS population* **Mean ± SD**	**Baclofen** N=87	**Placebo** N=84	**Means difference to placebo** [95%CI]	***p***
Baseline	**19.4 ± 6.7**	**17.4 ± 7.2**		
Change at Month 6	**-11.7 ± 9.6**	**-7.5 ± 8.4**	**-2.86** [-5.22 ; -0.51]	**0.017**

*Only patients with documented visits are taken into account



SUBGROUP OF PATIENTS WITH HIGH DRINKING RISK LEVEL AT BASELINE

POST HOC ANALYSIS

BASELINE ALCOHOL CONSUMPTION (TLFB)

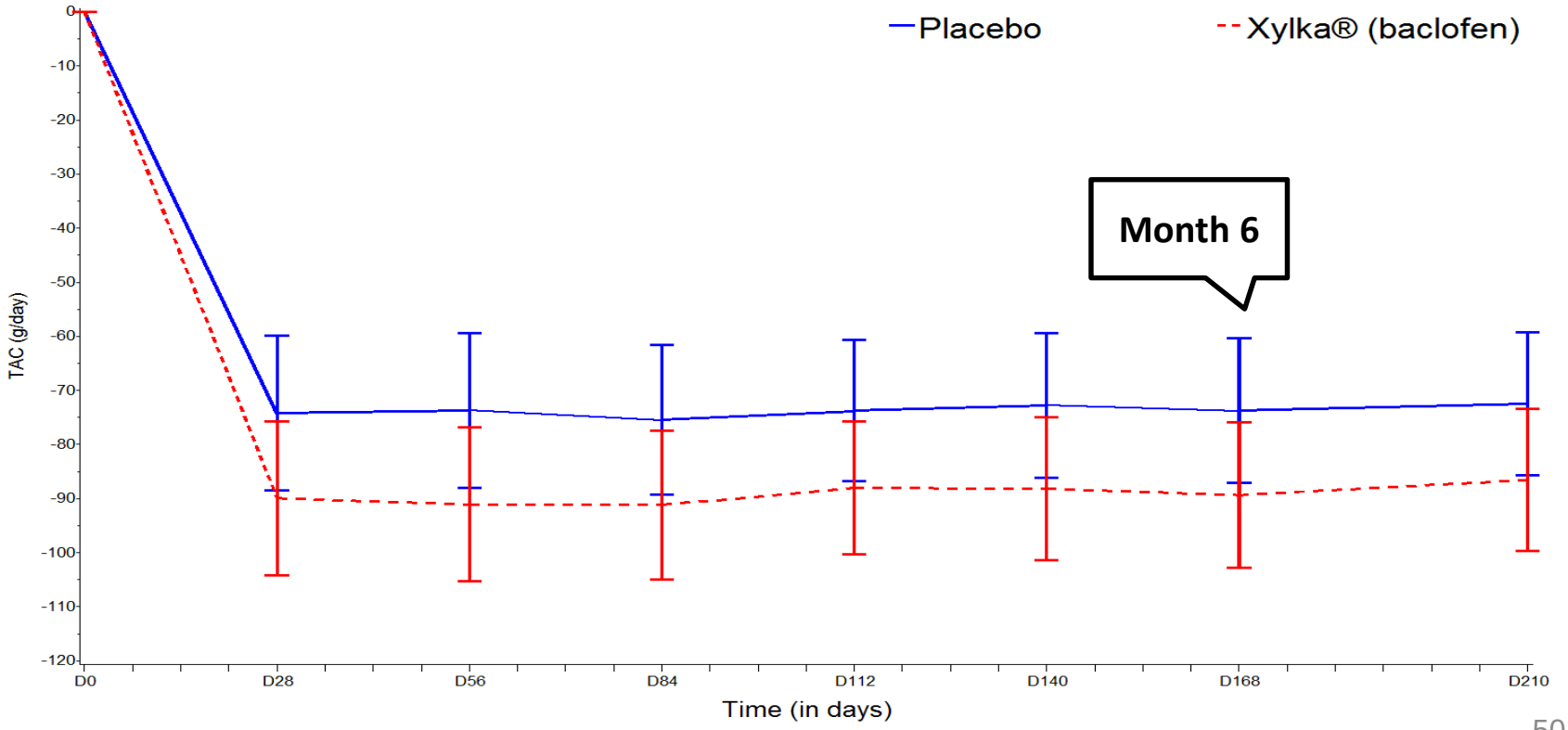
FAS population (N=215) Mean ± SD	Baclofen N= 106	Placebo N= 109
Total alcohol consumption (g/day) TAC	**123.6 ± 75.9**	**118.9 ± 62.0**
✓ Male	133.8 ± 81.5	129.6 ± 61.6
✓ Female	88.6 ± 35.2	96.2 ± 57.3
Heavy drinking days /28 days HDD	**23.8 ± 5.4**	**22.8 ± 6.2**
Abstinent days/28 days	2.0 ± 3.8	2.8 ± 5.0
Drinking risk level (WHO) % patients		
✓ High risk	43.4%	37.6%
✓ Very high risk	56.6%	62.4%

TAC - CHANGE FROM BASELINE

Adjusted change from baseline to month 6*

*calculated using generalized model with treatment group, drinking risk level at baseline and pooled centers as covariates

LSmeans [95%CI]	Baclofen	Placebo	Difference to placebo	*p*
TAC g/day	**-89.34** [-102.77;- 75.92]	**-73.74** [-87.12;- 60.36]	**-15.61** [-33.62; 2.41]	**0.089**

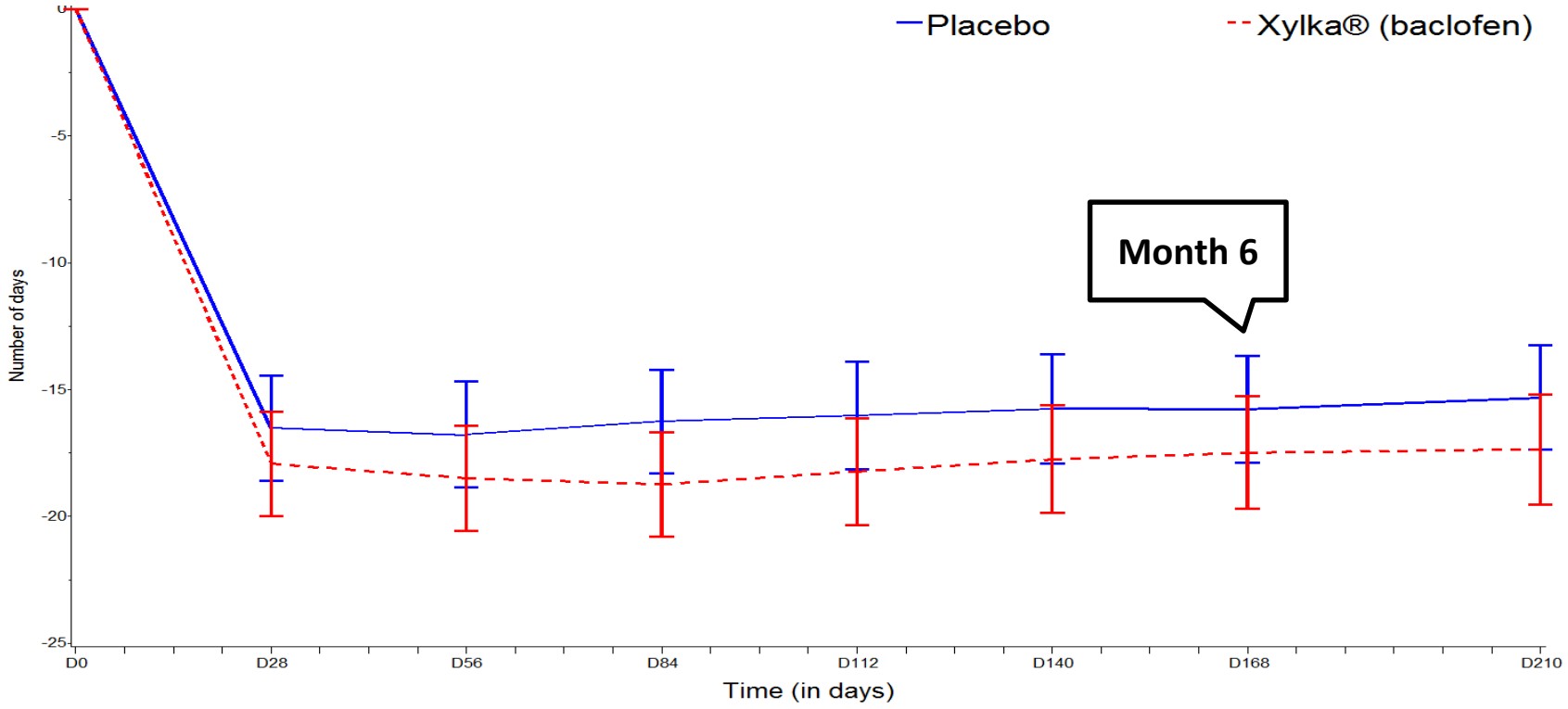


HDD - CHANGE FROM BASELINE

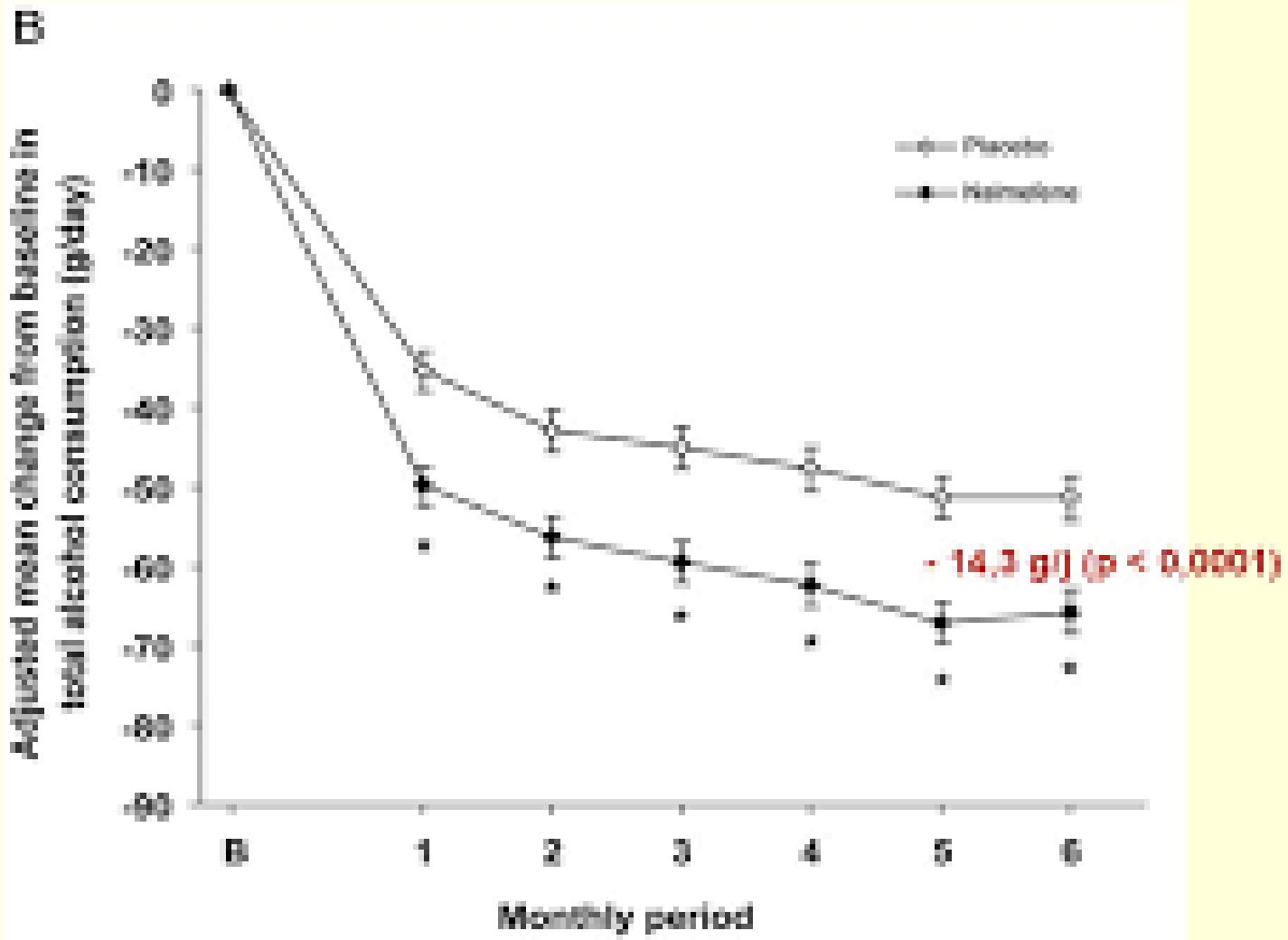
Adjusted change from baseline to month 6*

*calculated using generalized model with treatment group, drinking risk level at baseline and pooled centers as covariates

LSmeans [95%CI]	Baclofen	Placebo	Difference to placebo	*p*
HDD days/month	**-17.49** [-19.71;- 15.27]	**-15.77** [-17.89;- 13.66]	**-1.72** [-4.56; 1.12]	**0.236**



Nalmefene – ESENSE 1 + 2
Consommateurs à risque élevé (> 60 g H ; > 40 g F)



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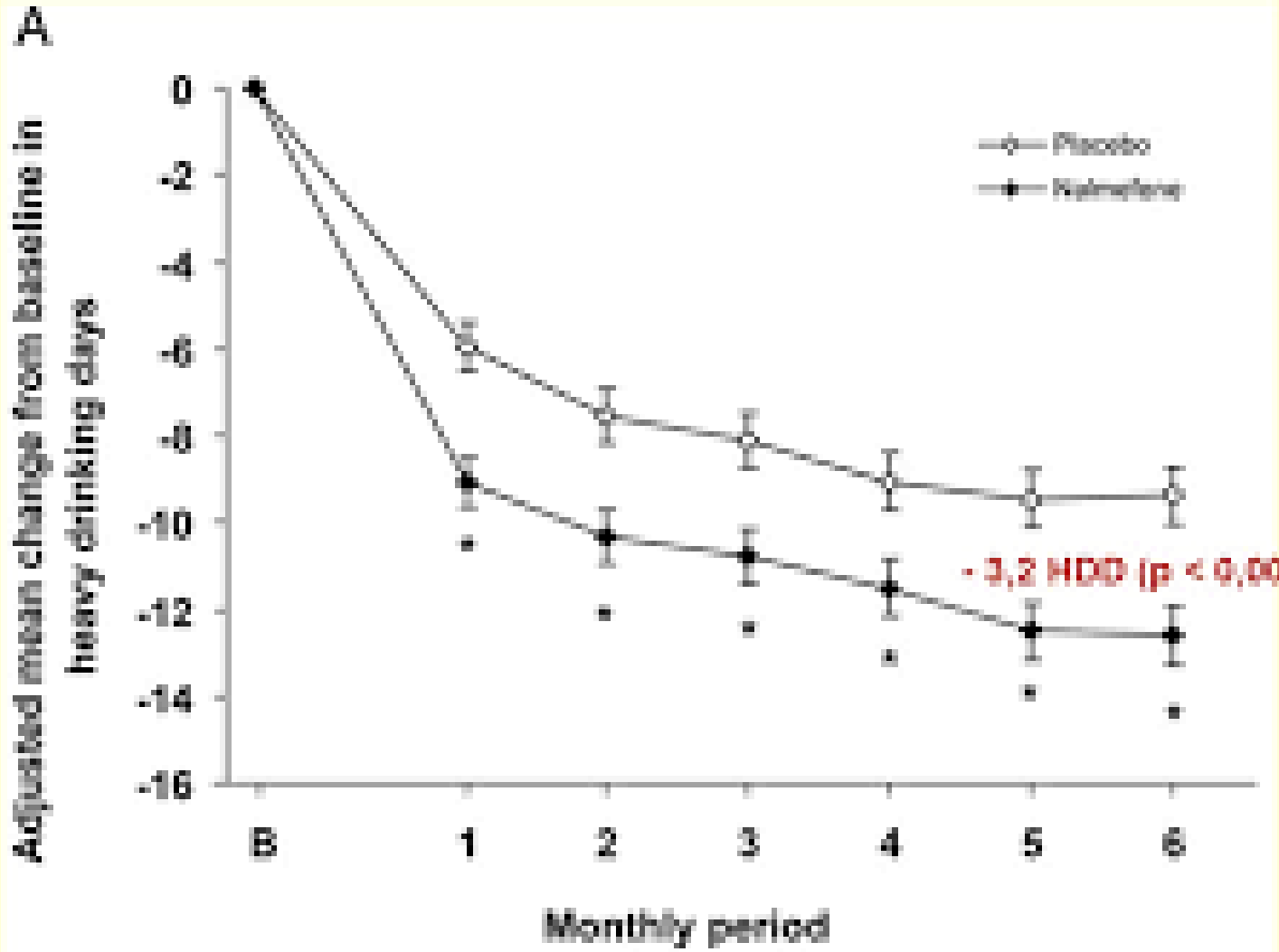


OCDS – CHANGE AT MONTH 6

Total OCDS score (0-40)				
FAS population* **Mean ± SD**	**Baclofen** N=58	**Placebo** N=54	**Means difference to placebo** [95%CI]	***p***
Baseline	**19.6 ± 6.6**	**18.9 ± 7.4**		
Change at Month 6	**-12.8 ± 8.8**	**-8.5 ± 9.2**	**-3.85** [-6.54 ; - 1.16]	**0.005**

*Only patients with documented visits are taken into account

Effect size 0.56

SAFETY
ADVERSE EVENTS

ADVERSE EVENTS

SAF population (N=316)	Baclofen N=157	Placebo N=159
At least one AE (% patients)	96.8%	91.8%
Number of AE (N events)	1245	863
AE related to treatment	672	342
At least one SAE (% patients)	12.7%	16.4%
Number of SAE (N events)	40	43
SAE related to treatment	14	11

MOST FREQUENT RELATED ADVERSE EVENTS

Percentage of patients SAF population	Baclofen N=157	Placebo N=159
Somnolence	43.95%	23.90%
Asthenia	29.30%	21.38%
Dizziness	28.66%	10.69%
Sleep disorders	19.74%	13.84%
Paresthesia	12.74%	3.14%
Headache	12.10%	8.81%
Nausea	9.55%	4.40%
Muscle spasms	9.55%	1.26%
Tinnitus	9.55%	1.89%
Disturbance in attention	7.64%	3.14%
Hyperhidrosis	7.01%	0.63%
Dysgeusia/ageusia	7.01%	0.63%

WHAT CAN WE CONCLUDE FROM ALPADIR STUDY ?

MAINTENANCE OF ABSTINENCE

- ✓ Baclofen not superior to placebo at the target dose of 180 mg/day
- ✓ Results very far from hypothesis : abstinence rates very low, much lower than expected in power calculation
- ✓ Specific French media context and Recommandation Temporaire d'Utilisation : possible shift of expectations from abstinence to alcohol reduction

REDUCTION OF ALCOHOL CONSUMPTION

Important and persistent **placebo response** for all criteria of reduction of alcohol consumption

Reduction in TAC

✓ Observed in both groups, more important with baclofen and of clinical significance:

- 55g for the global population (- 44g in placebo group)

- 89g for patients with high drinking risk level (- 74g in placebo group)

✓Difference in the change from baseline not statistically different between groups but ALPADIR not powered for reduction of alcohol consumption

Reduction in HDD

- **9,9 days** in global population (-8,7 in placebo)
- **17,5 days** in high drinking risk level (-15,8 in placebo)

SOME POINTS OF DISCUSSION

Posology

A maximal and stable clinical response observed as soon as the end of the first month of treatment in both groups (90 mg/day) ►High dose concept to be discussed

“Anti craving” effect

A more important decrease of OCDS with baclofen

Correlation with TAC reduction

►In favor of the anti craving effect

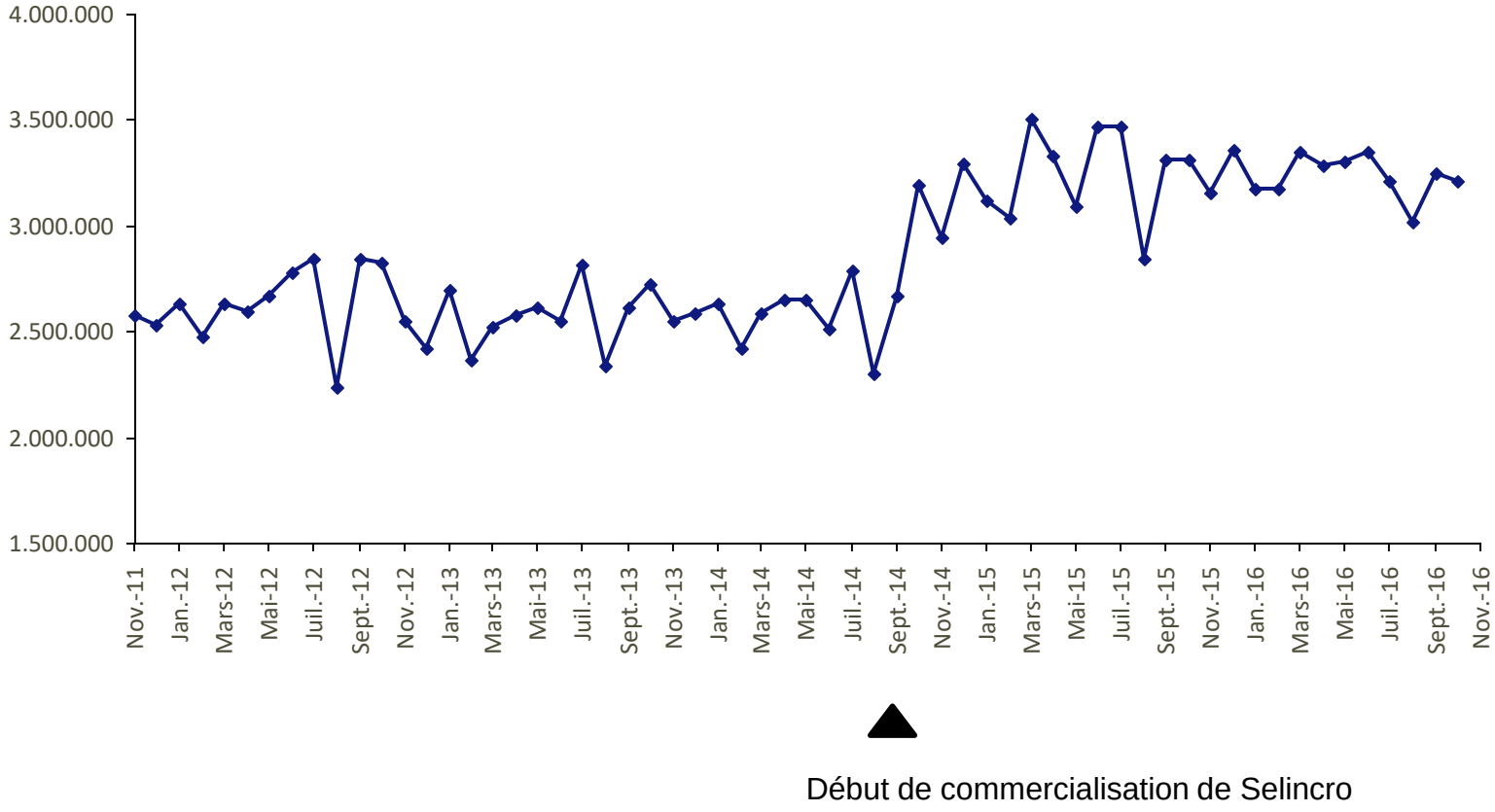
Safety

A good safety profile, no major safety concern, with 180mg and after detoxification

Need for a larger pharmacological arsenal in AUD

With different mechanisms of action the place of an effective craving-reliever in the pharmacotherapy of AUD

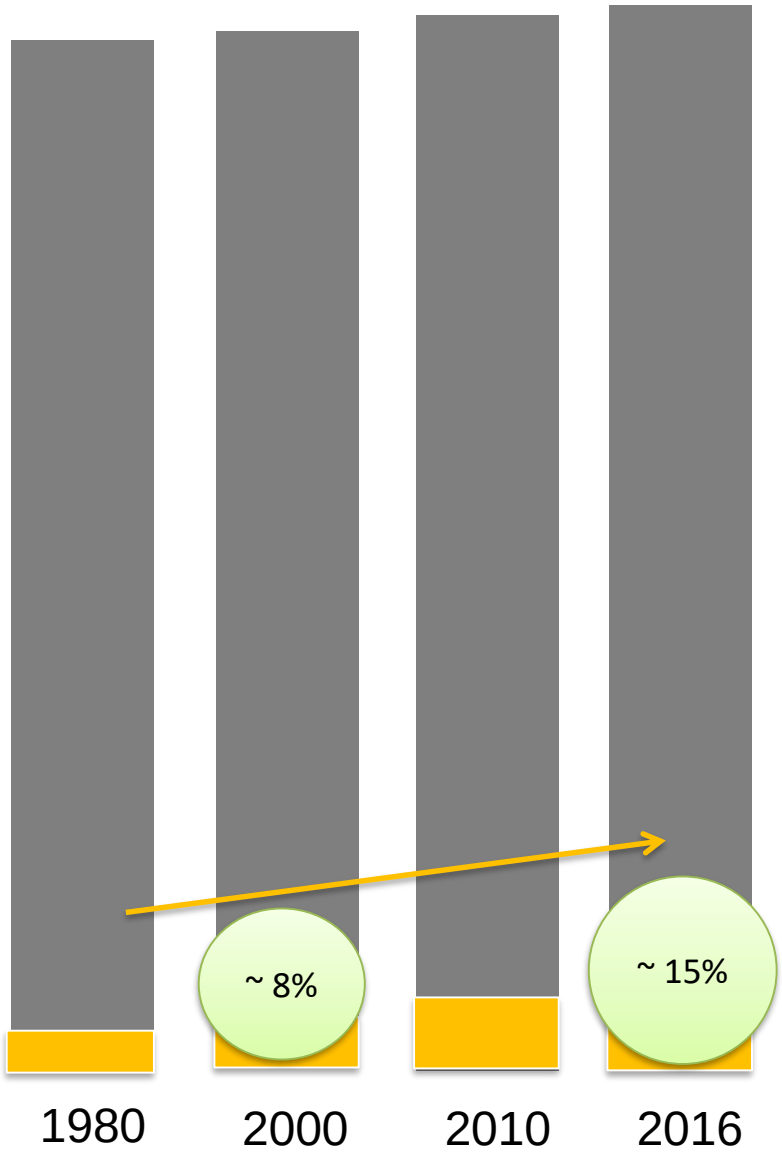
VOLUME DU MARCHE ALCOOL (en jours de traitement)



Début de commercialisation de Selincro

Source: GERS Ville oct 2016 (N07E+ baclofène dans l'indication Alcool)

QUID DU GAP DE TRAITEMENT ?



2 000 000

patients non pris en charge

1 000 000

BACK UP

OTHER ALCOHOL CONSUMPTION ENPOINTS

FAS population	Baclofen	Placebo	p
Responders * at month 6 % of patients [95%CI]**	**80.8%** [76.4; 85.2]	**74.7%** [69.9; 79.6]	0.144
Time to first drink (days)*** Median [95%CI]	**35** [33;39]	**33** [31;38]	0.412
Time to first heavy drink (days)*** Median [95%CI]	**85** [60;112]	**63** [49;76]	0.221
Patients without HDD during 20 weeks (post hoc analysis) % of patients [95%CI]**	**43.1%** [37.6; 48.6]	**37.6%** [32.2; 42.9]	0.273

*** Responder: very high risk drinking at baseline to medium or below at month 6; high or medium risk drinking at baseline to low at month 6**

Premature termination before D29 ➔ non responder

**** mean of the 5 imputed data sets**

*****excluding the grace period**

OTHER SECONDARY ENDPOINTS

QUESTIONNAIRES AND SCALES ► HAD-CGI-AlQoL9

►Improved over time (decreased for HAD and CGI, increased for AlQoL9)

►Scores in favor of baclofen but no statistical difference between groups

LIVER BIOMARKERS ►GGT-CDT

►More important decrease over time in baclofen patients

Change from baseline	Means difference	p value
CDT (%)	-0.47	0.077
GGT (log value)	-0.20	0.012