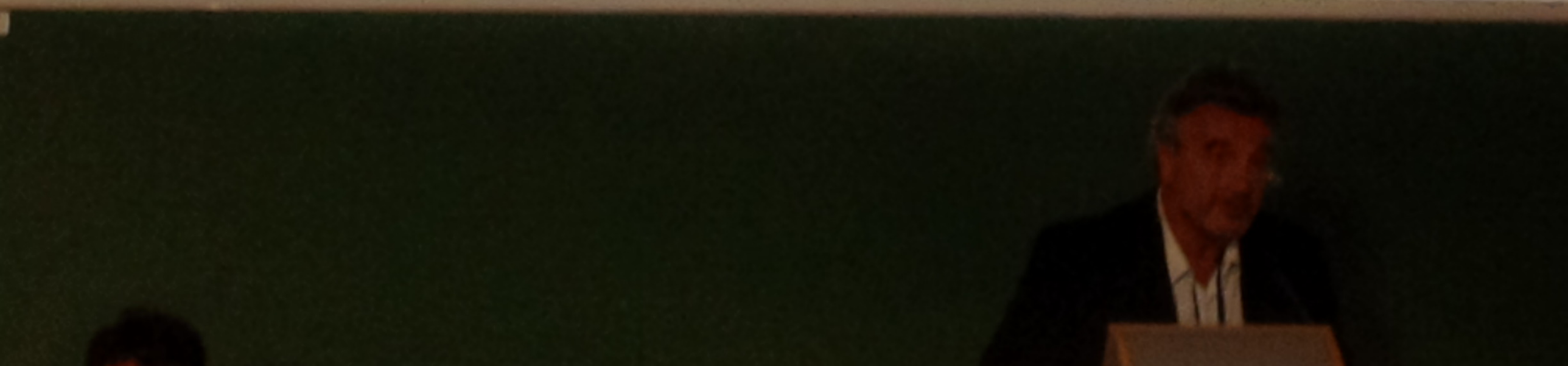
Berlin - 3 september 2016

ALPADIR

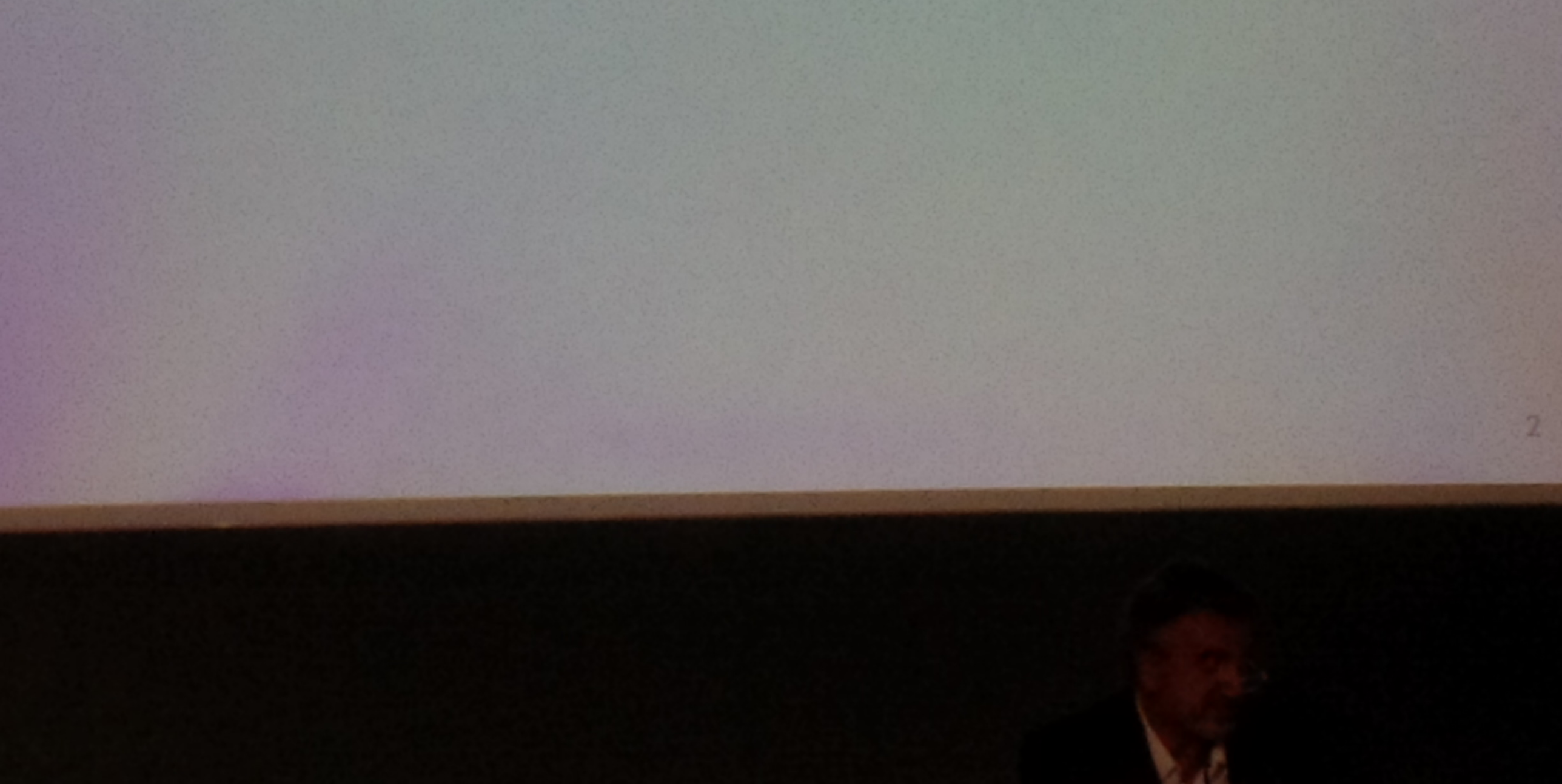
A randomized, double blind, placebo- controlled efficacy study of high-dose baclofen in alcohol dependent patients

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



CONFLICT OF INTEREST

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



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%

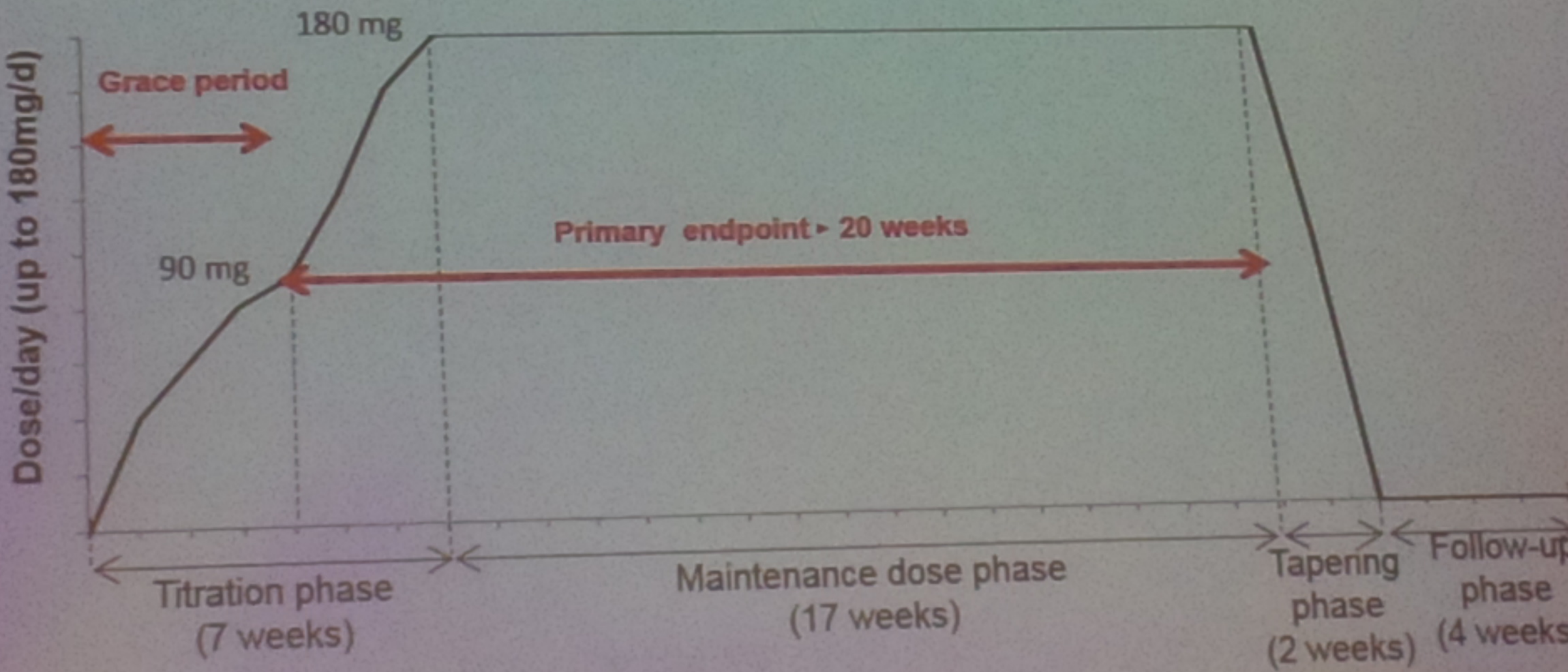
ENDPOINTS AND TREATMENT

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

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

ASELINE 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% → 68.4	43.9% → 70.4

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**
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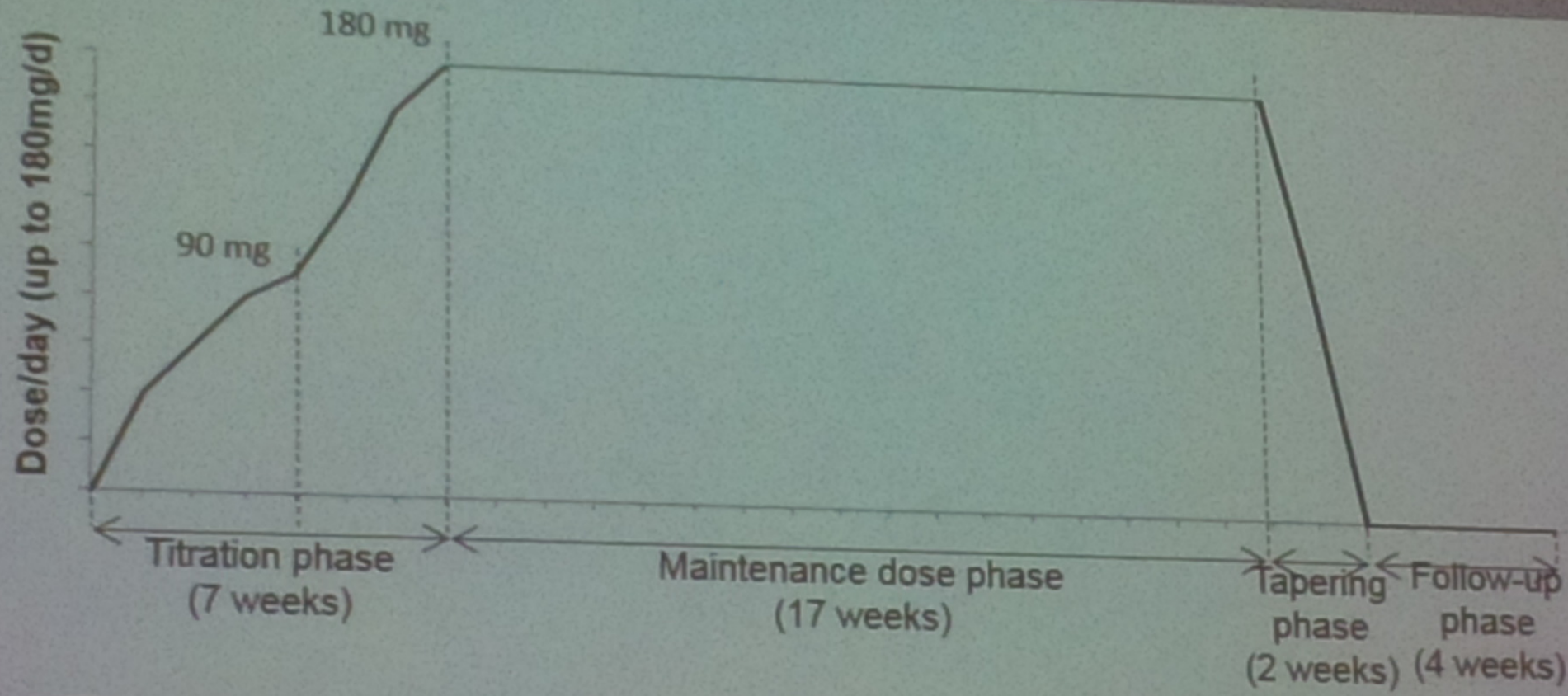
POSOLOGY



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

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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

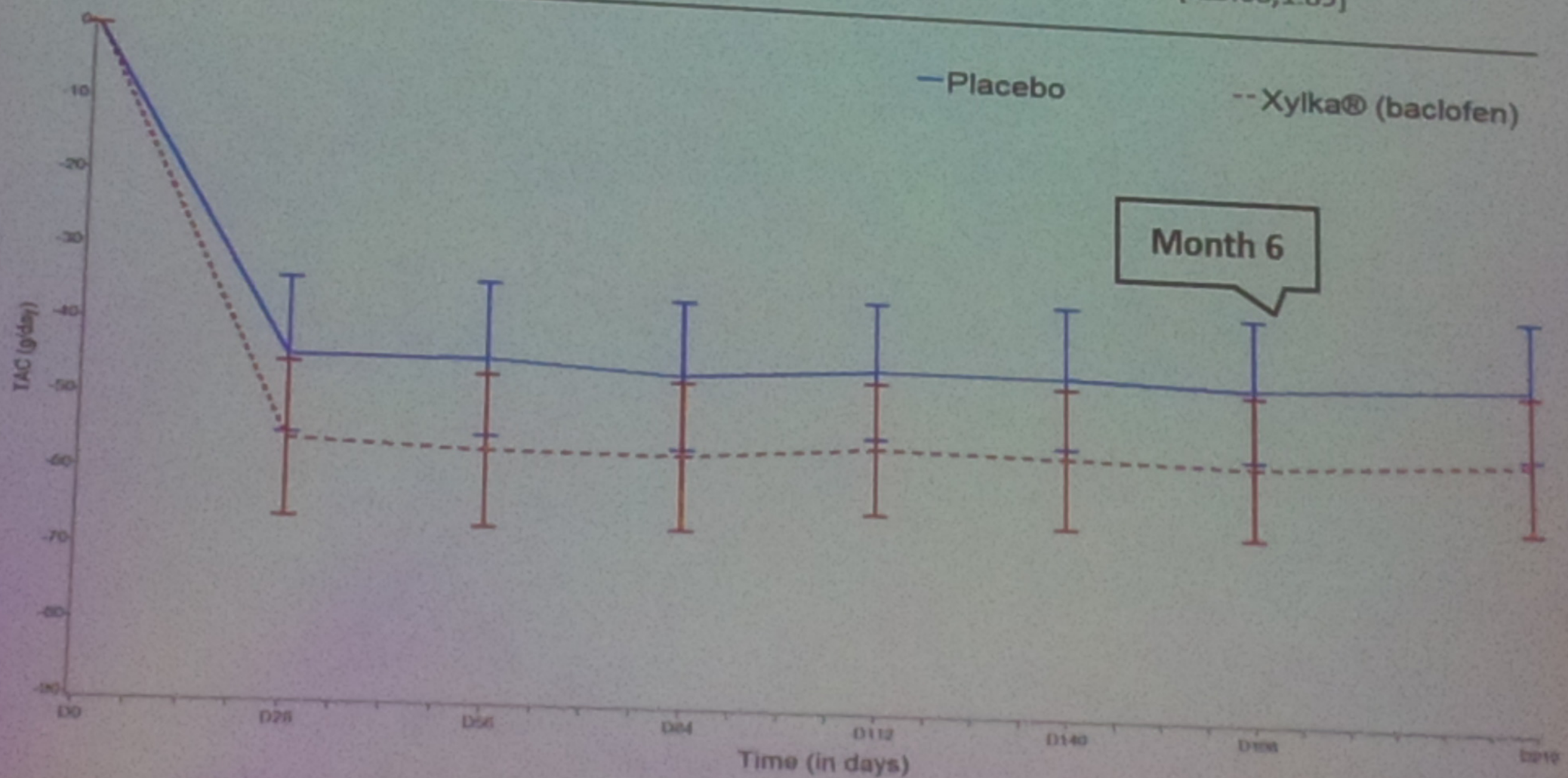
*Mean of the five imputed data sets

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



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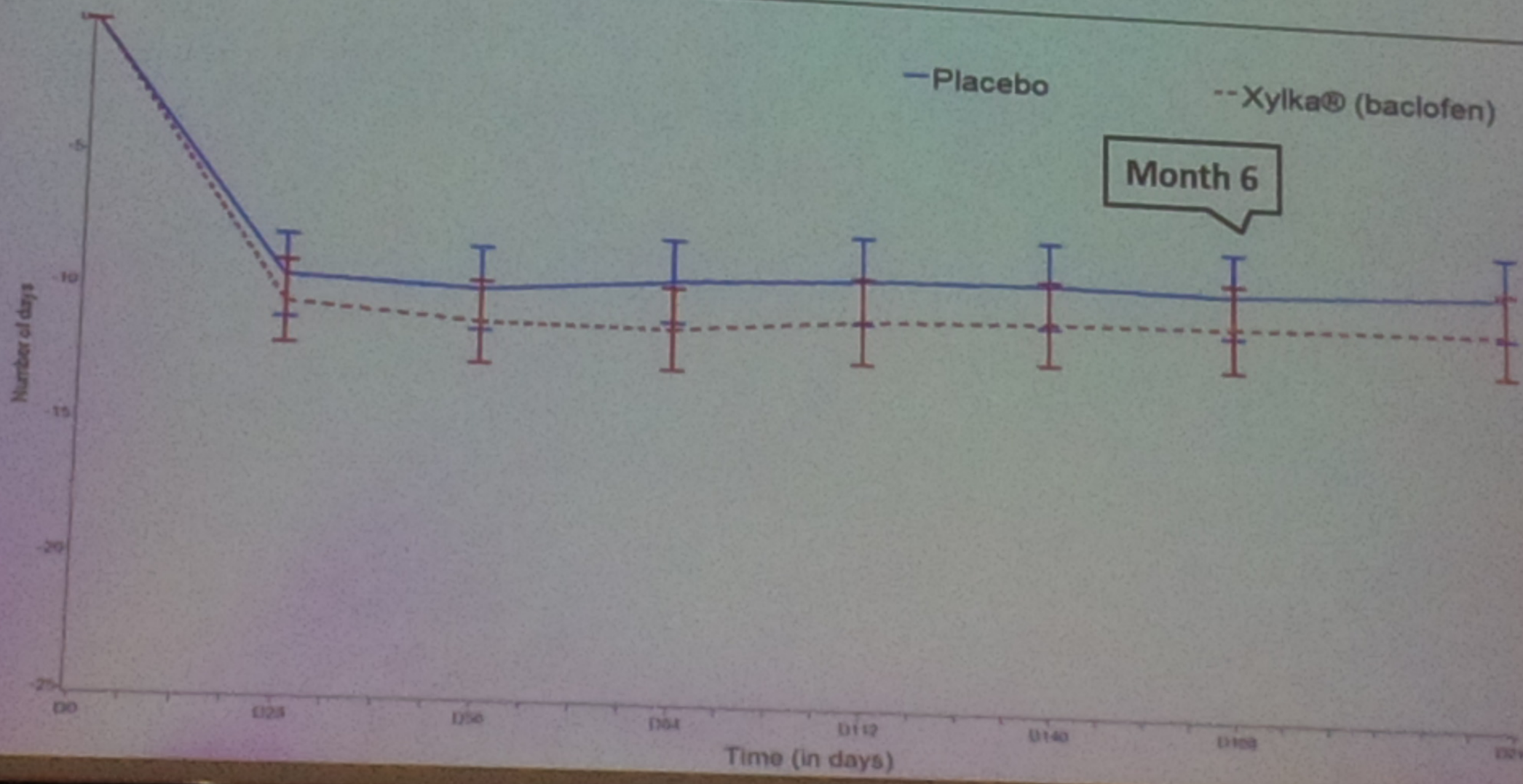
HDD - CHANGE FROM BASELINE

Adjusted change from baseline to month 6*

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

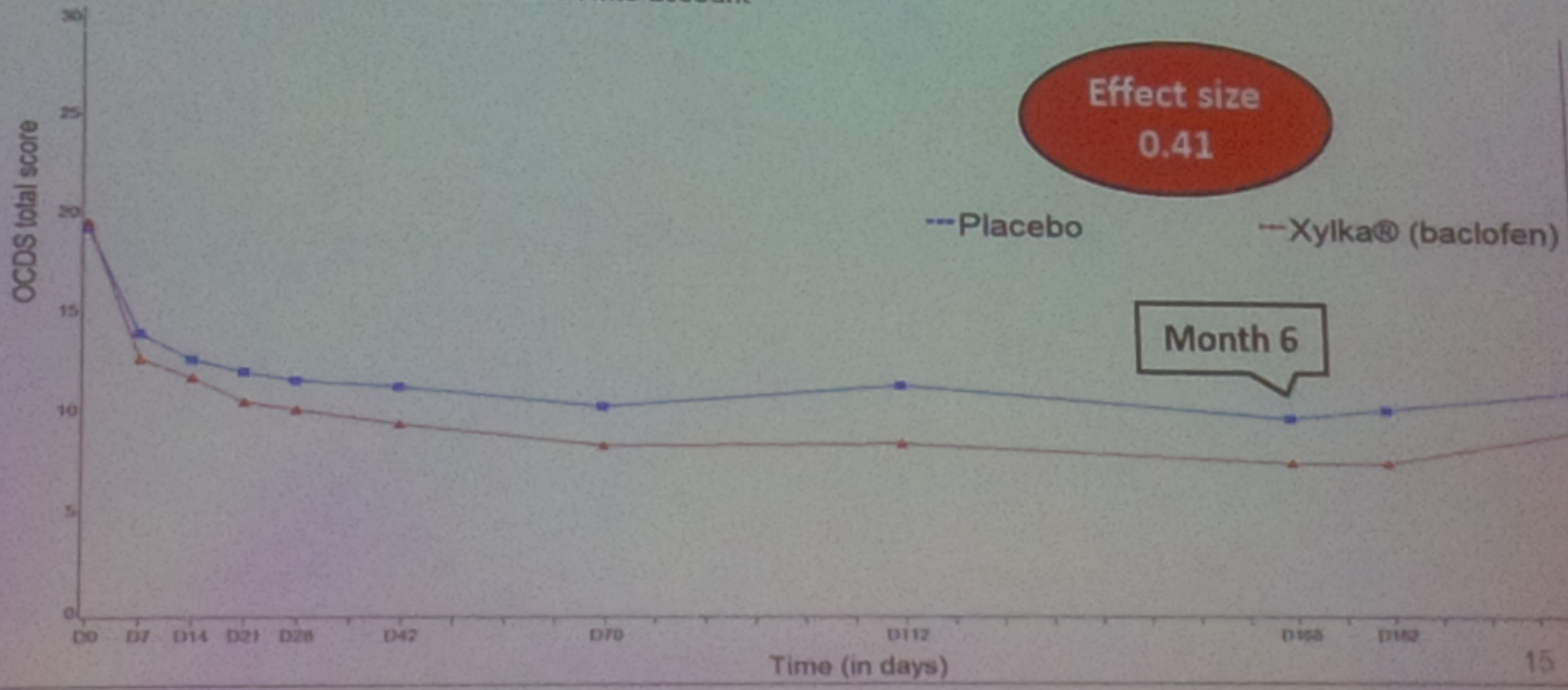
LSmeans [95%CI]	Baclofen	Placebo	Difference to placebo	*p*
HDD days/month	-9.9 [-11.69;-8.29]	-8.70 [-10.34;-7.07]	-1.29 [-3.38;0.81]	0.228



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)

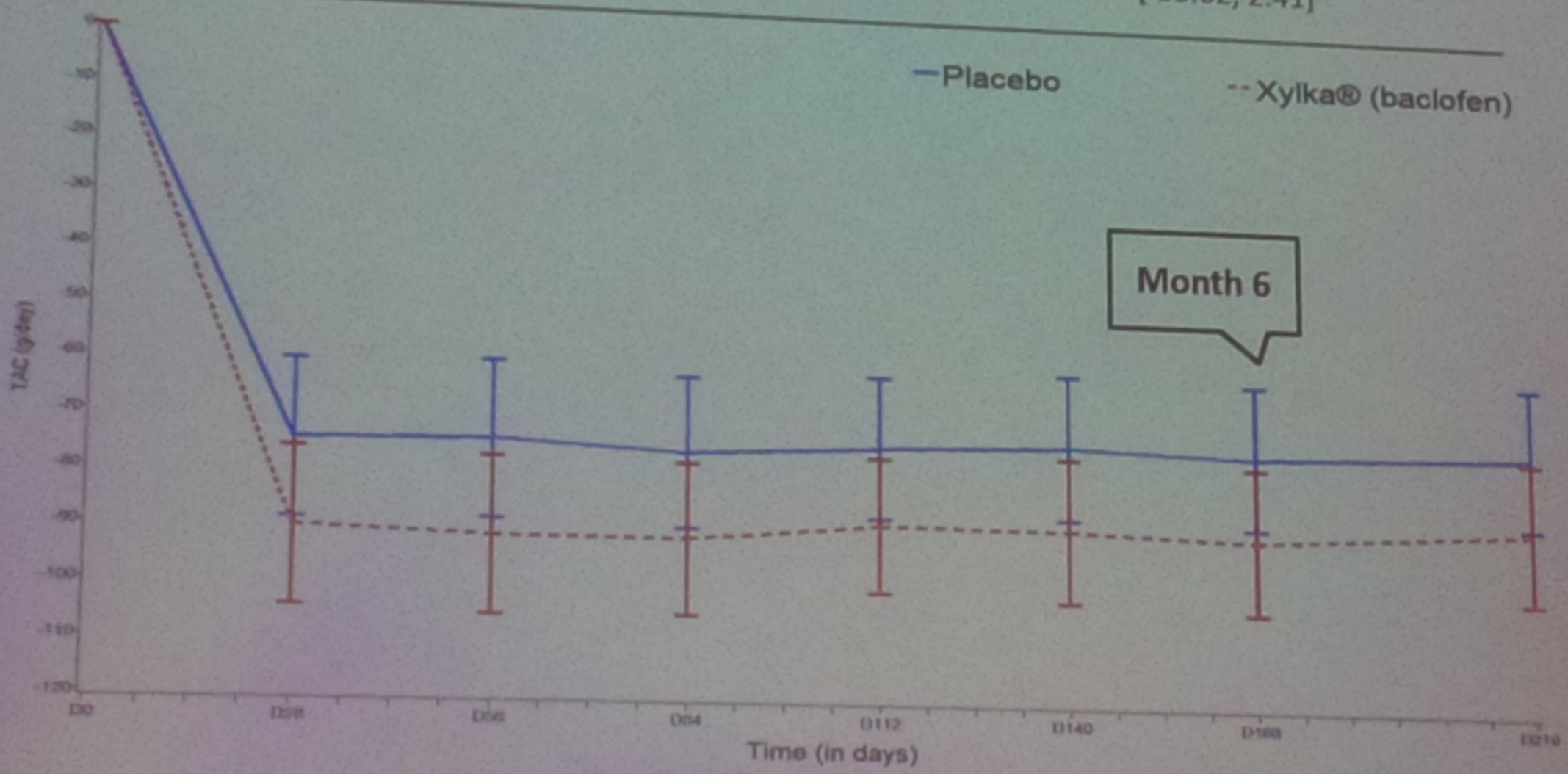
FAS population (N=215) Mean ± SD	Baclofen N= 106	Placebo N= 109
Total alcohol consumption (g/day) TAC	**123.6 ± 75.9**	**118.9 ± 62.0**
✓ Male	133.8 ± 81.5	129.6 ± 61.6
✓ Female	88.6 ± 35.2	96.2 ± 57.3
Heavy drinking days /28 days HDD	**23.8 ± 5.4**	**22.8 ± 6.2**
Abstinent days/28 days	2.0 ± 3.8	2.8 ± 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

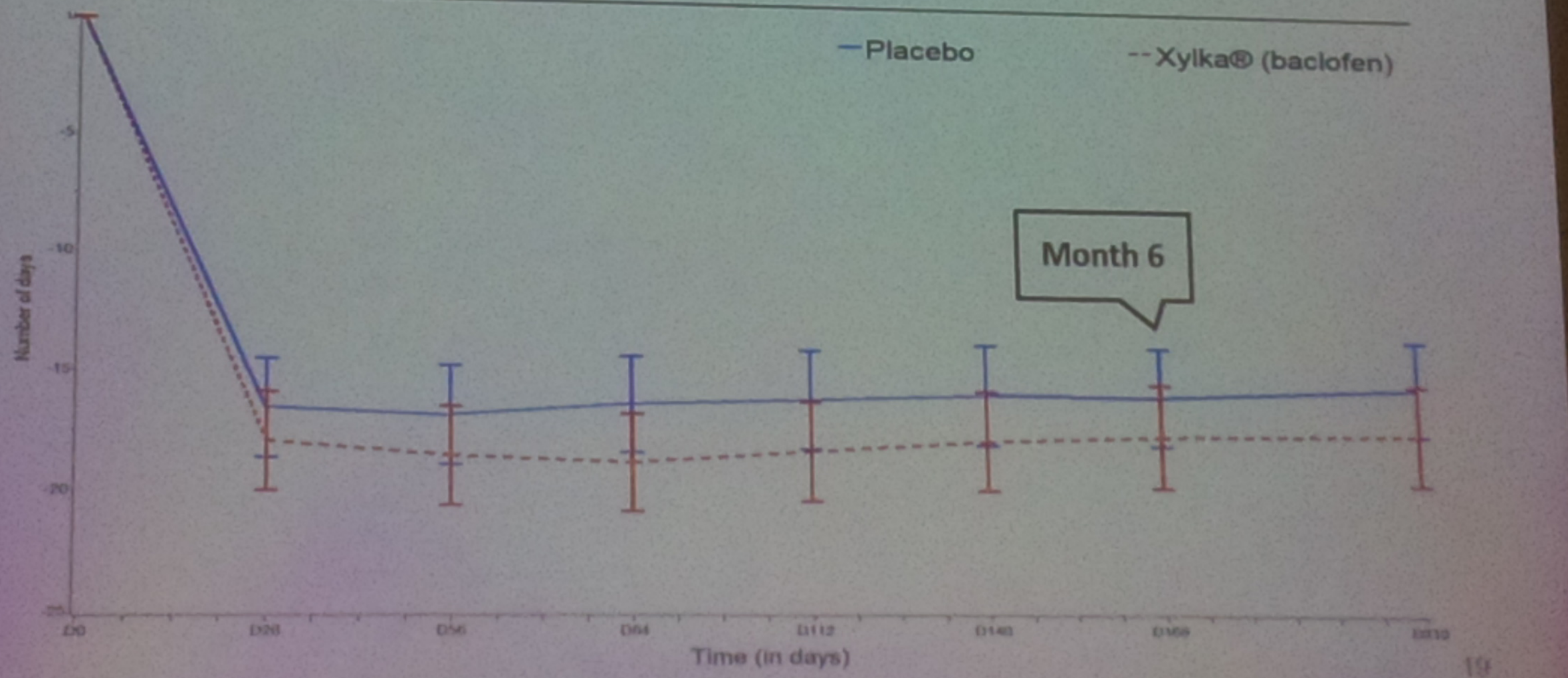


HDD - CHANGE FROM BASELINE

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**



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

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REDUCTION OF ALCOHOL CONSUMPTION

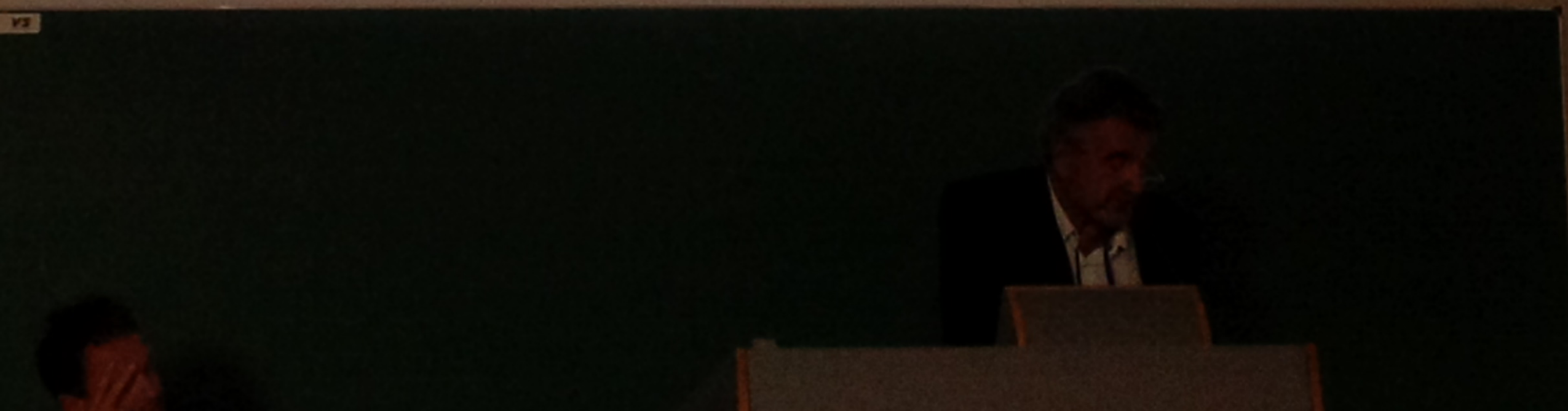
Important and persistent **placebo response** for all criteria of reduction of alcohol consumption

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