High-Dose Baclofen for the Treatment of Alcohol Dependence

The BACLAD study

of Psychiatry
ité Mitte

NeuroCure
Exzellenzcluster

Charité

BACKGROUND

- Up to 85 % of alcohol-dependent patients relapse after detoxification
  (Helzer et al., 1985)

- Only a few substances approved for the treatment of AUD

- Modest effects of current pharmacotherapies
  (Rösner et al., 2010; Jonas et al., 2014)

CHARIT

BACLOFEN

- Selective γ-aminobutyric acid (GABA)-B receptor agonist
- Approved for the treatment of spasticity resulting from various neurological conditions
- $T_{1/2}$: 6,8 ± 0,7 h
- Tmax: 1,4 - 2,8 h
- Oral bioavailability > 85%
- > 80% renal elimination

CHARITÉ

BACLOFEN: PRECLINICAL EVIDENCE

- GABA-B receptor involved in alcohol related behaviors (Colombo et al., 2002, 2004)

- GABA-B receptors located in several brain areas including the mesolimbic dopaminergic reward system (Bowery et al., 1987)

- Baclofen modulates dopaminergic transmission in the mesolimbic reward system (Fadda et al., 2003)

- Baclofen suppresses the acquisition and maintenance of alcohol drinking behavior in rats (Agabio & Colombo 2014)

CHARITÉ

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.

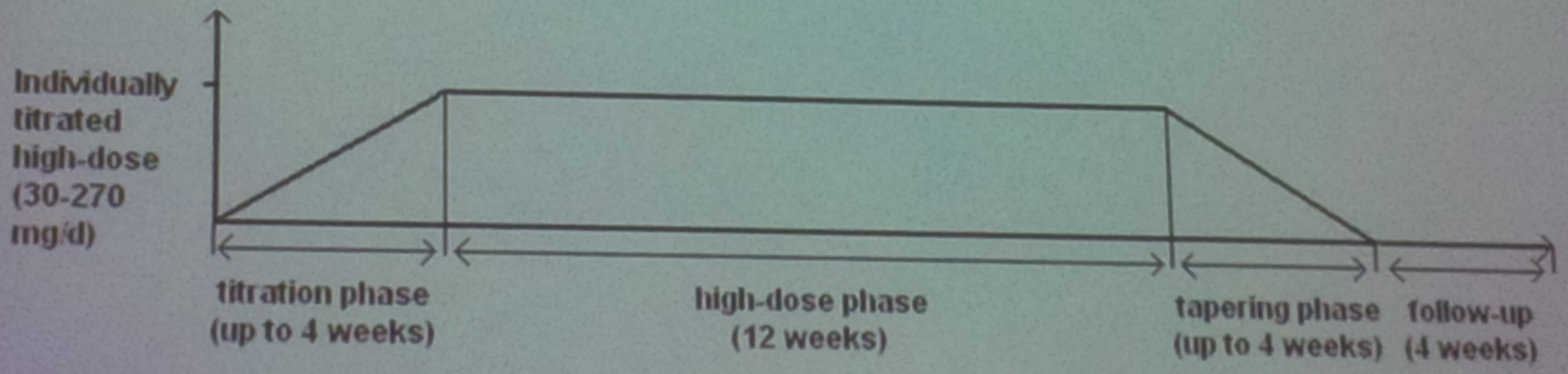
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

RATIONALE

- Evidence from preclinical and clinical studies for the efficacy and safety of baclofen in AUD
- RCTs using low to medium dosages (30-80 mg/d) have shown mixed results
- Several positive case reports of high-dose baclofen (up to 270 mg/d) in AUD (Ameisen et al., 2005)
- Low ability of baclofen to cross the blood brain barrier (Taira, 2009)

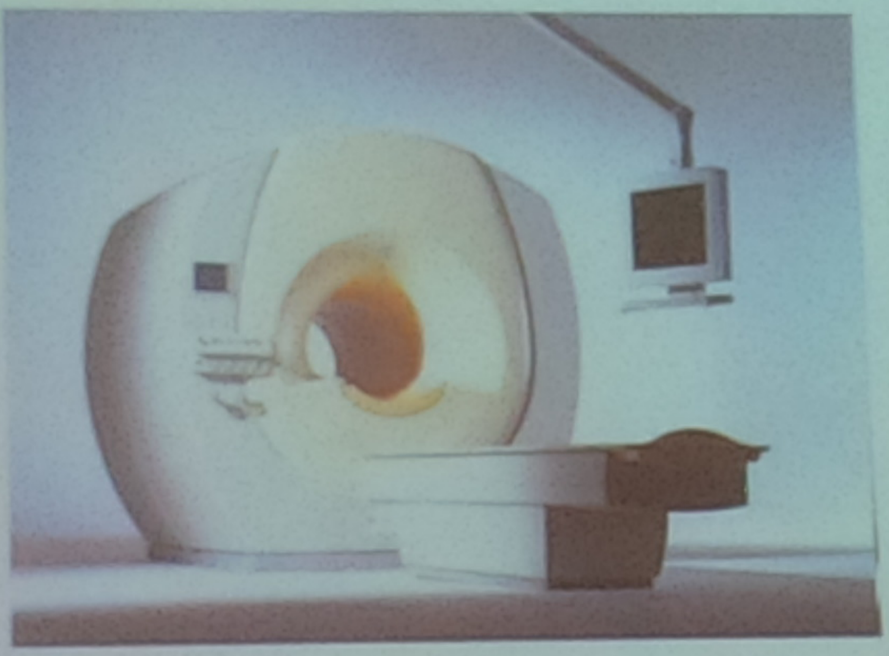
CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

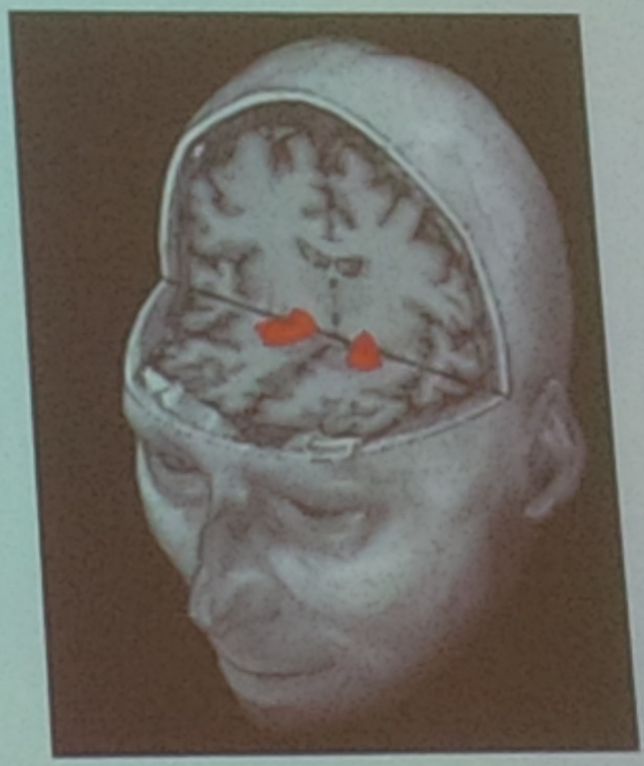
TRIAL PROFILE

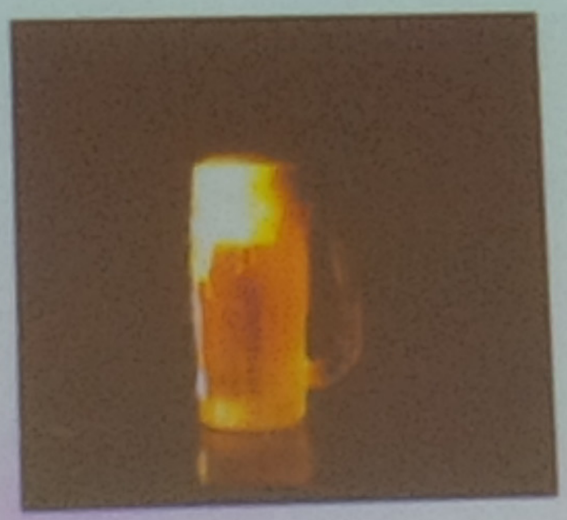


CHARITÉ

FMRI CUE-REACTIVITY







+

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

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

CHARITÉ

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

CHARITÉ

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

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

CLINICAL CHARACTERISTICS

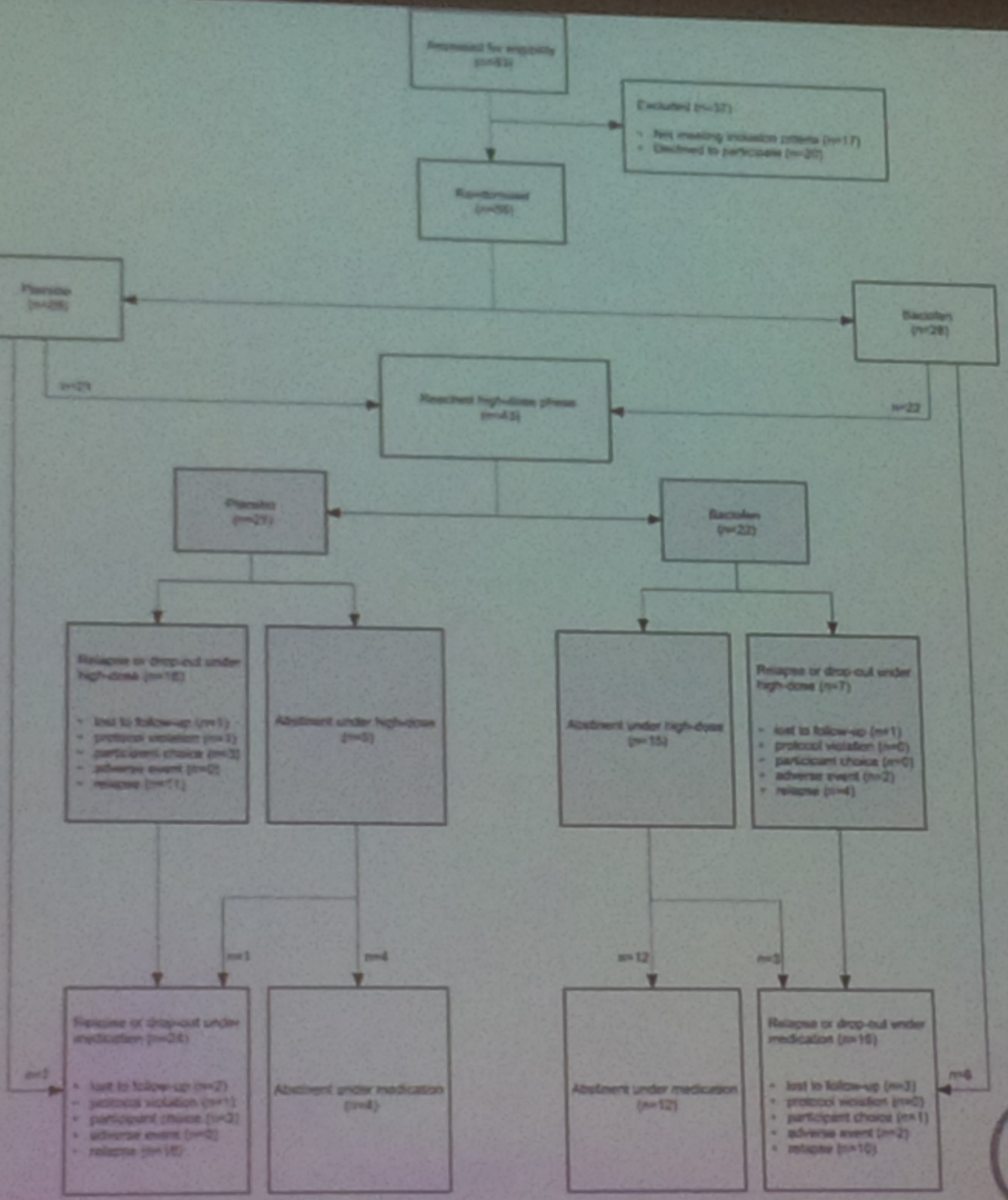
Characteristics	Placebo	Baclofen	*p* Value
Sex [*n* (%)]			
Male	19 (67.9)	20 (71.4)	n.s.[a]
Female	9 (32.1)	8 (28.6)	
Age [mean ± SD (range)]	45.6 ± 7 (29-64)	47.4 ± 7 (32-59)	n.s.[b]
Highest school qualification [*n* (%)]			n.s.[a]
Secondary modern school-leaving certificate, year 5-9	1 (3.6)	0 (0)	
Secondary modern school-leaving certificate, year 5-10	1 (3.6)	1 (3.6)	
University-entrance diploma	1 (3.6)	2 (7.1)	
Technical college	15 (53.6)	21 (75)	
University degree	10 (35.7)	4 (14.3)	
Employment status [*n* (%)]			n.s.[a]
Employed	15 (53.6)	17 (60.7)	
Unemployed	13 (46.4)	11 (39.3)	
Marital status [*n* (%)]			n.s.[a]
Married	11 (39.3)	5 (17.9)	
Separated	0 (0)	3 (10.7)	
Divorced	4 (14.3)	8 (28.6)	
Unmarried	13 (46.4)	12 (42.9)	
Smoker [*n* (%)]	18 (64.3)	17 (60.7)	n.s.[a]
Years of hazardous alcohol consumption [mean (SD)]	11.5 (7.3)	13.9 (10.1)	n.s.[b]
Alcohol consumption (grams) per day before inclusion [mean (SD)]	191.6 (94.8)	206.2 (94.1)	n.s.[b]
Days of abstinence at study inclusion (Baseline) [mean (SD)]	12 (4.9)	12.4 (4.6)	n.s.[b]
Number of previous detoxifications [*n* (%)]			n.s.[a]
One	7 (25)	11 (39.3)	
2-5	16 (57.1)	12 (42.9)	
More than 5	5 (17.9)	5 (17.9)	
Positive family history regarding alcohol dependence (first-degree relatives) [*n* (%)]	15 (53.6)	18 (64.3)	n.s.[a]
ADS [mean (SD)]	15.8 (5.1)	16.6 (6.2)	n.s.[b]

[a]Exact Chi-square test.
[b]Exact Mann-Whitney *U* test.

CLINICAL CHARACTERISTICS

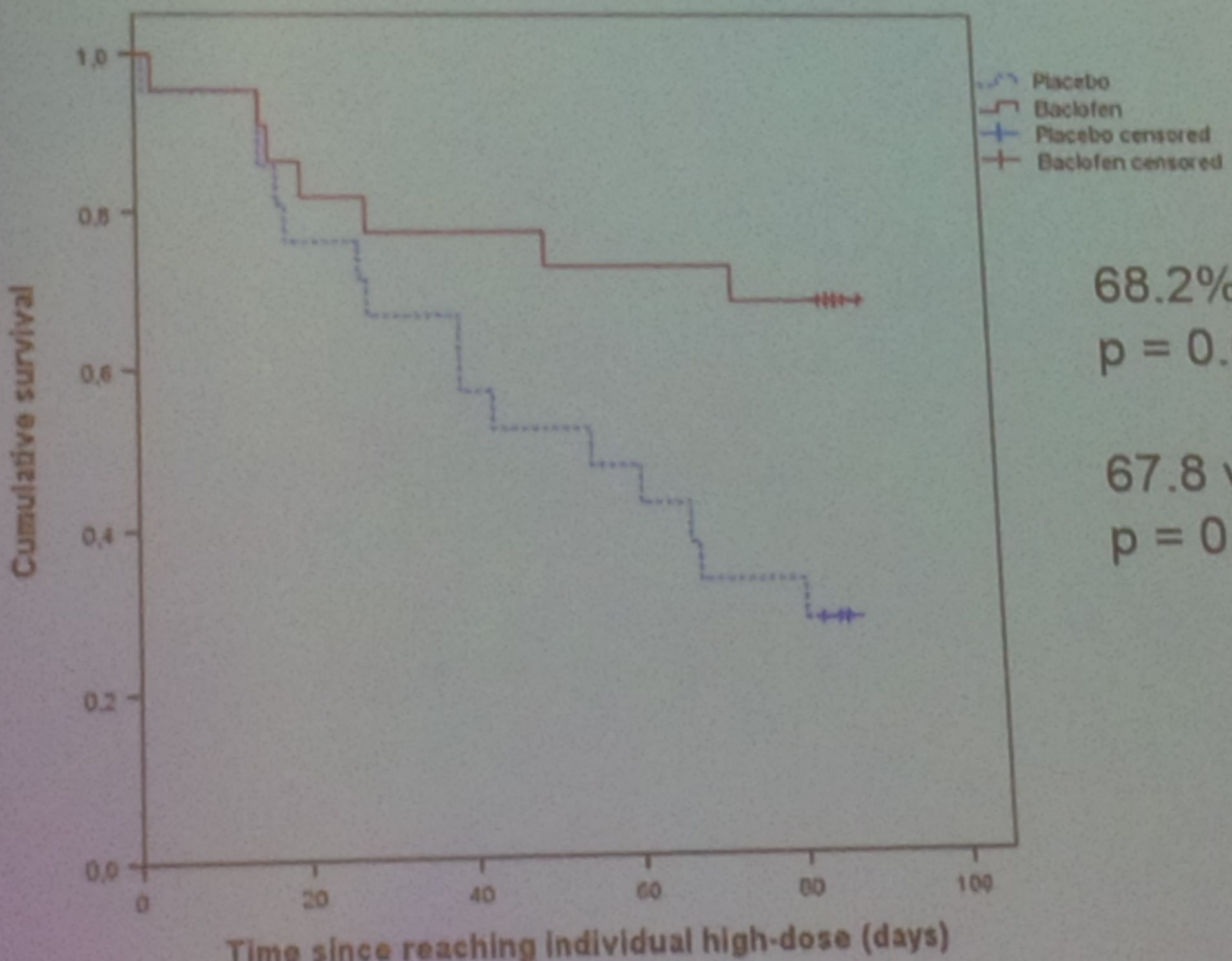
Characteristics	Placebo	Baclofen	p Value
Sex [*n* (%)]			
Male	19 (67.9)	20 (71.4)	n.s.[a]
Female	9 (32.1)	8 (28.6)	
Age [mean ± SD (range)]	45.6 ± 7 (29-64)	47.4 ± 7 (32-59)	n.s.[b]
Highest school qualification [*n* (%)]			n.s.[a]
Secondary modern school-leaving certificate, year 5-9	1 (3.6)	0 (0)	
Secondary modern school-leaving certificate, year 5-10	1 (3.6)	1 (3.6)	
University-entrance diploma	1 (3.6)	2 (7.1)	
Technical college	15 (53.6)	21 (75)	
University degree	10 (35.7)	4 (14.3)	
Employment status [*n* (%)]			n.s.[a]
Employed	15 (53.6)	17 (60.7)	
Unemployed	13 (46.4)	11 (39.3)	
Marital status [*n* (%)]			n.s.[a]
Married	11 (39.3)	5 (17.9)	
Separated	0 (0)	3 (10.7)	
Divorced	4 (14.3)	8 (28.6)	
Unmarried	13 (46.4)	12 (42.9)	
Smoker [*n* (%)]	18 (64.3)	17 (60.7)	n.s.[a]
Years of hazardous alcohol consumption [mean (SD)]	11.5 (7.3)	13.9 (10.1)	n.s.[b]
Alcohol consumption (grams) per day before inclusion [mean (SD)]	191.6 (94.8)	206.2 (94.1)	n.s.[b]
Days of abstinence at study inclusion (Baseline) [mean (SD)]	12 (4.9)	12.4 (4.6)	n.s.[b]
Number of previous detoxifications [*n* (%)]			n.s.[a]
One	7 (25)	11 (39.3)	
2-5	16 (57.1)	12 (42.9)	
More than 5	5 (17.9)	5 (17.9)	
Positive family history regarding alcohol dependence (first-degree relatives) [*n* (%)]	15 (53.6)	18 (64.3)	n.s.[a]
ADS [mean (SD)]	15.8 (5.1)	16.6 (6.2)	n.s.[b]

[a]Exact Chi-square test.
[b]Exact Mann Whitney *U* test.


Assessed for eligibility (n=63)
Excluded (n=37)
Not meeting inclusion criteria (n=17)
Declined to participate (n=20)
Randomized (n=58)
Placebo (n=29)
Baclofen (n=28)
n=29
Reached high-dose phase (n=43)
n=22
Placebo (n=27)
Baclofen (n=22)
Relapse or drop-out under high-dose (n=16)
lost to follow-up (n=1)
protocol violation (n=1)
participant choice (n=3)
adverse event (n=2)
relapse (n=11)
Abstinent under high-dose (n=5)
Abstinent under high-dose (n=15)
Relapse or drop-out under high-dose (n=7)
lost to follow-up (n=1)
protocol violation (n=0)
participant choice (n=0)
adverse event (n=2)
relapse (n=4)
n=1
n=4
n=12
n=3
Relapse or drop-out under medication (n=24)
lost to follow-up (n=2)
protocol violation (n=1)
participant choice (n=2)
adverse event (n=0)
relapse (n=19)
Abstinent under medication (n=4)
Abstinent under medication (n=12)
Relapse or drop-out under medication (n=16)
lost to follow-up (n=3)
protocol violation (n=0)
participant choice (n=1)
adverse event (n=2)
relapse (n=10)
n=1
n=6

HIGH-DOSE PHASE

a

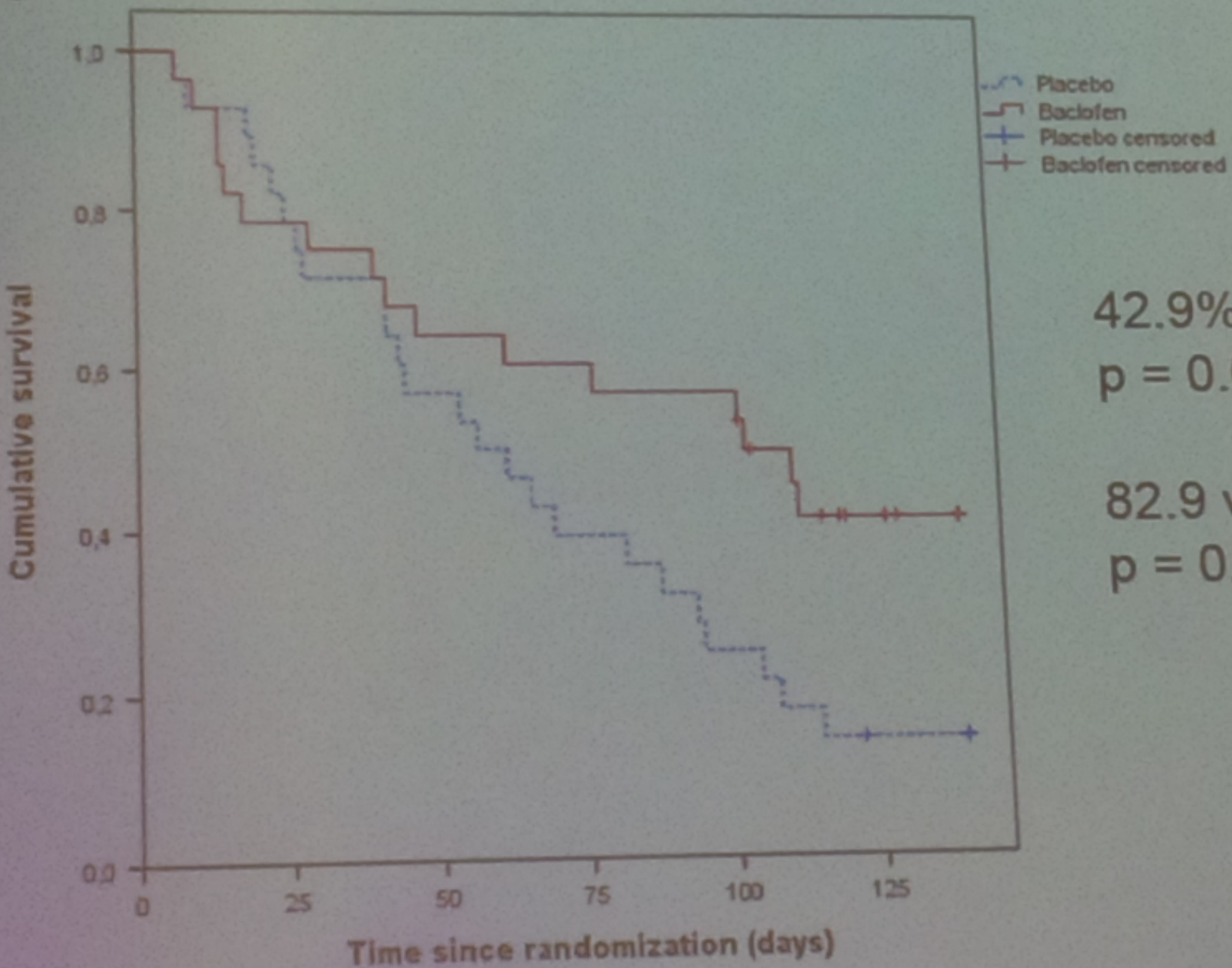


68.2% vs. 23.8%
p = 0.014

67.8 vs. 51.8 days
p = 0.047

COMPLETE MEDICATION PHASE

b



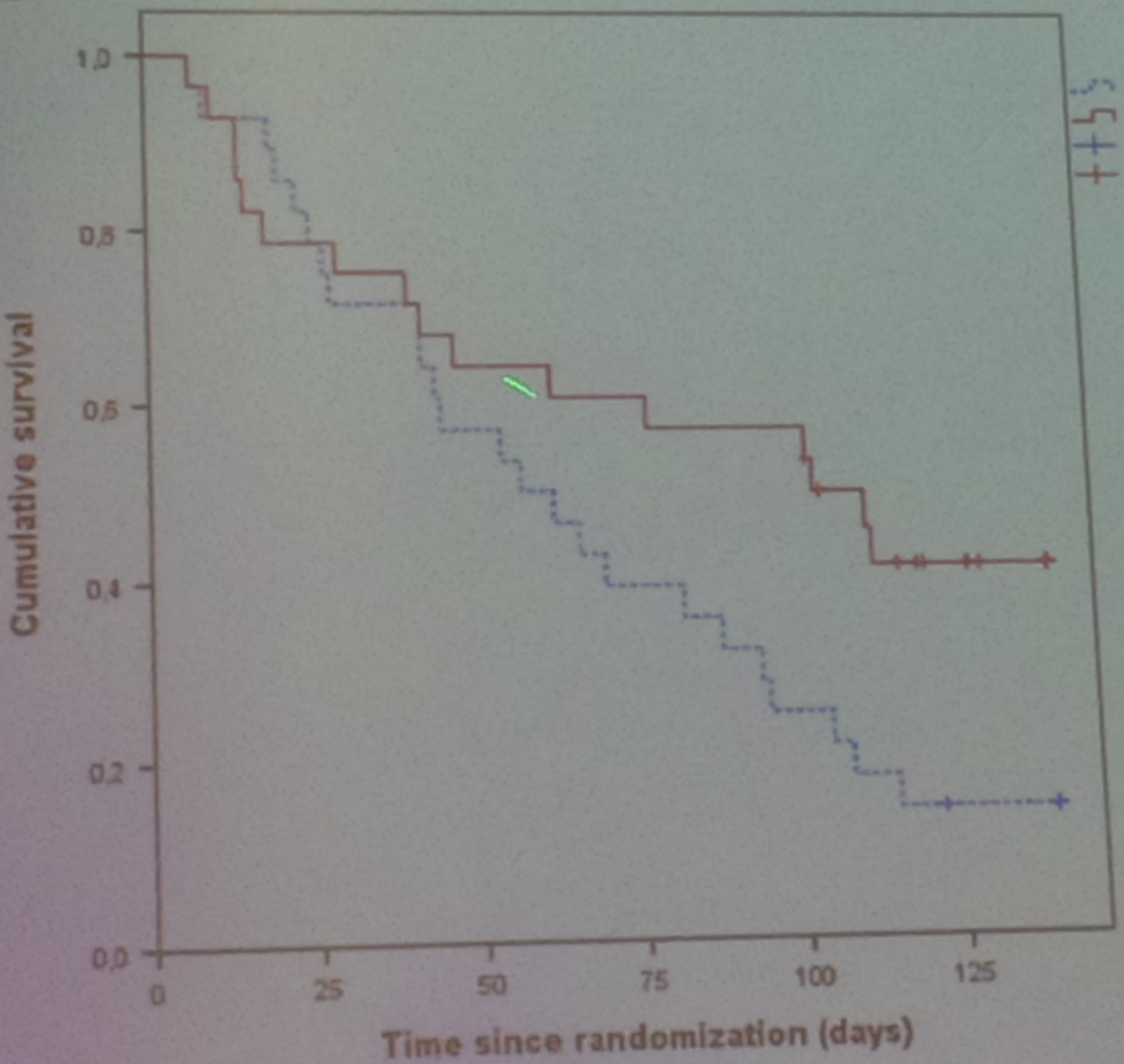
42.9% vs. 14.3%
p = 0.037

82.9 vs. 66.8 days
p = 0.241

CHARI

COMPLETE MEDICATION PHASE

b

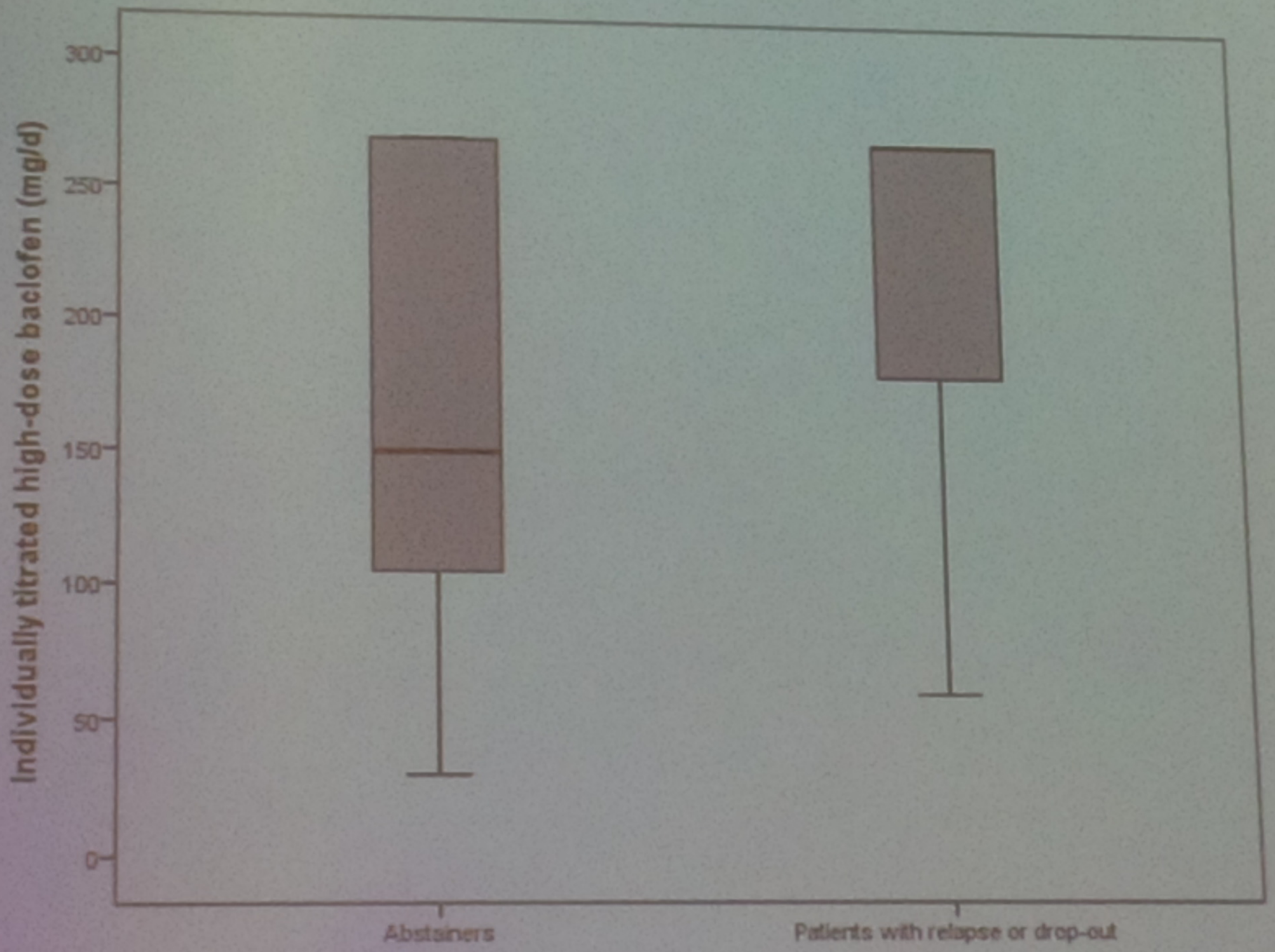


42.9% vs. 14.3%
p = 0.037

82.9 vs. 66.8 days
p = 0.241

CHARI

DOSE-RESPONSE EFFECT?



ADVERSE EVENTS

Adverse event	Placebo [*n* (%)]	Baclofen [*n* (%)]	Total [*n* (%)]	*p* Value[a]
Headache	7 (25.0)	4 (14.3)	11 (19.6)	0.503
Fatigue	7 (25.0)	13 (46.4)	20 (35.7)	0.162
Sleep disturbances	4 (14.3)	9 (32.1)	13 (23.2)	0.205
Muscle weakness	3 (10.7)	6 (21.4)	9 (16.1)	0.469
Vertigo/dizziness	0 (0)	5 (17.9)	5 (8.9)	0.051
Visual disturbances	2 (7.1)	5 (17.9)	7 (12.5)	0.422
Muscle pain	3 (10.7)	0 (0)	3 (5.3)	0.236
Fasciculations	1 (3.6)	4 (14.3)	5 (8.9)	0.352
Common cold/infection	11 (39.3)	1 (3.6)	12 (21.4)	0.002
Depressed mood/anxiety	2 (7.1)	3 (10.7)	5 (8.9)	1.00
Gastrointestinal symptoms	3 (10.7)	1 (3.6)	4 (7.1)	0.611
Urgency	0 (0)	4 (14.3)	4 (7.1)	0.111
Hypertension	2 (7.1)	3 (10.7)	5 (8.9)	1.00
Tingling sensation	0 (0)	3 (10.7)	3 (5.3)	0.236
Pain (diverse)	8 (28.6)	4 (14.3)	12 (21.4)	0.329

[a]Exact Chi-square test.

CHARITÉ

ADVERSE EVENTS

Adverse event	Placebo [*n* (%)]	Baclofen [*n* (%)]	Total [*n* (%)]	*p* Value[a]
Headache	7 (25.0)	4 (14.3)	11 (19.6)	0.503
Fatigue	7 (25.0)	13 (46.4)	20 (35.7)	0.162
Sleep disturbances	4 (14.3)	9 (32.1)	13 (23.2)	0.205
Muscle weakness	3 (10.7)	6 (21.4)	9 (16.1)	0.469
Vertigo/dizziness	0 (0)	5 (17.9)	5 (8.9)	0.051
Visual disturbances	2 (7.1)	5 (17.9)	7 (12.5)	0.422
Muscle pain	3 (10.7)	0 (0)	3 (5.3)	0.236
Fasciculations	1 (3.6)	4 (14.3)	5 (8.9)	0.352
Common cold/infection	11 (39.3)	1 (3.6)	12 (21.4)	0.002
Depressed mood/anxiety	2 (7.1)	3 (10.7)	5 (8.9)	1.00
Gastrointestinal symptoms	3 (10.7)	1 (3.6)	4 (7.1)	0.611
Urgency	0 (0)	4 (14.3)	4 (7.1)	0.111
Hypertension	2 (7.1)	3 (10.7)	5 (8.9)	1.00
Tingling sensation	0 (0)	3 (10.7)	3 (5.3)	0.236
Pain (diverse)	8 (28.6)	4 (14.3)	12 (21.4)	0.329

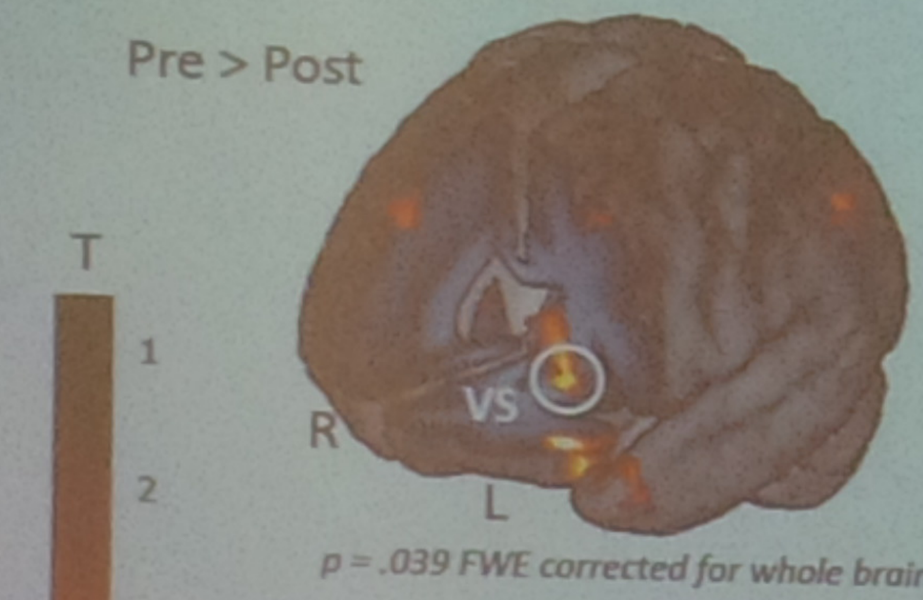
[a]Exact Chi-square test.

CHARITÉ

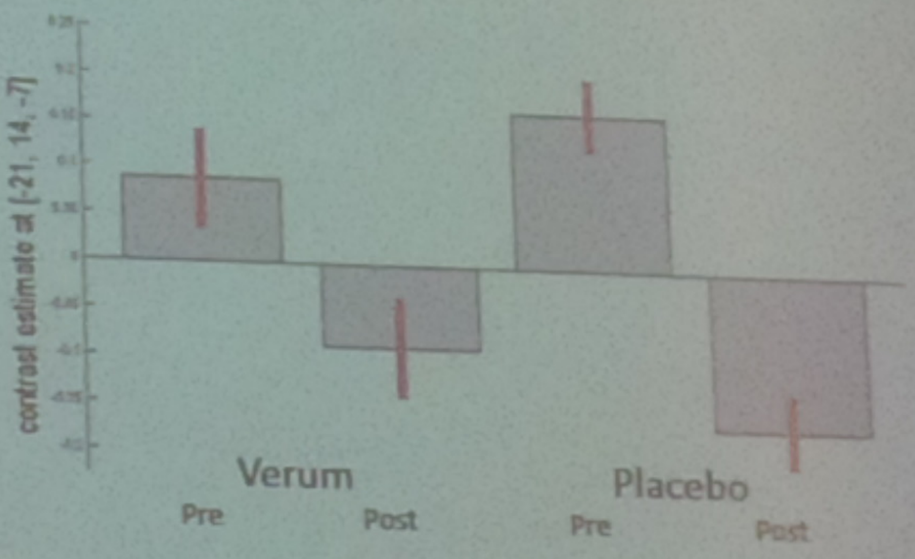
FMRI CUE-REACTIVITY

CHARITÉ

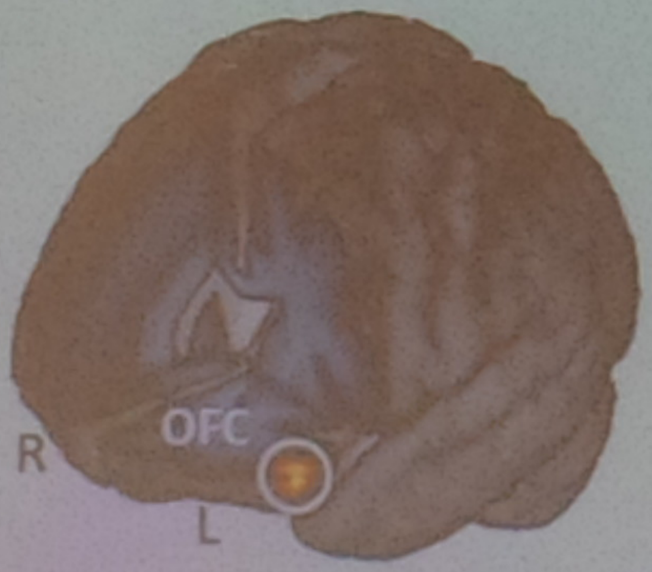
Pre > Post



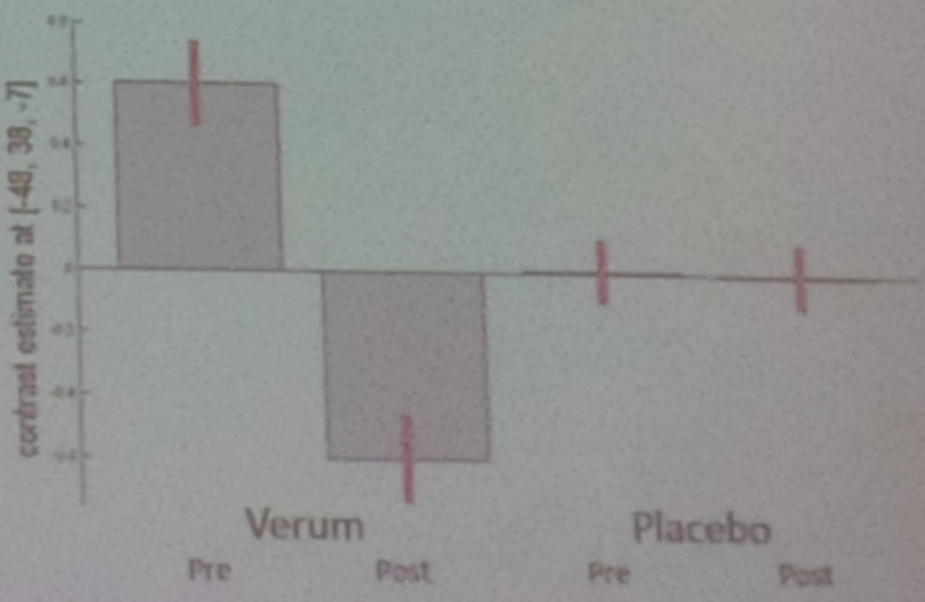
p = .039 FWE corrected for whole brain



Verum (Pre>Post) > Placebo (Pre>Post)



p = .006 FWE corrected for OFC-ROI



Beck et al., in preparation

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

CHARITÉ

QUESTIONS

- Replication of results
- Responding subtype
- Role of composition
- Dosing
- Reduction of alcohol consumption

CHARITÉ