Regulatory (EMA) Guidance on AD Medications

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EUROPEAN MEDICINES AGENCY
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Agenda

- **EMA Guideline of September 2010**
  - background / scope
  - treatment goals
    relapse prevention vs harm reduction
  - outcome measures / endpoints
- **Nalmefene**
- **Current regulatory perspective**

Background

- **AD as major public health problem;**
  prevalence of AD in men 5-6%, 1-2% in women
- **Evidence for alcohol-related harm (WHO 2000)**
- **Despite the great burden of the disease:**
  poor means of pharmacological intervention adjunct to psychosocial counselling

Drinking Risk Levels (DRL)

- **Strong correlation between the extent of AC and the risk of developing dependence & physical harm**
- **Categorisation of AC into different health risk levels (WHO 2000, English DR et al. 1995)**

WHO-Criteria for risk of consumption on a single drinking day in relation to acute problems

	Males	Females
Low Risk	1 to 40g,	1 to 20g
Medium Risk	41 to 60g,	21 to 40g
High Risk	61 to 100g	41 to 60g
Very High Risk	101+g	61+g

WHO-Criteria for risk of chronic harm

	Males	Females
Low Risk	1 to 40g,	1 to 20g
Medium Risk	41 to 60g,	21 to 40g
High Risk	61+ g	41+ g

Focus of the Guideline

- On products developed as an aid to achieve and maintain abstinence in patients with AD.
- This includes
  - products to prevent relapses after initiated abstinence and
  - products leading to clinically significantly reduced AC as an intermediate goal (harm reduction approach) on the way to full abstinence

Endpoints for Abstinence

- **Relapse prevention trial:**
  abstinent & fully detoxified at baseline
- **Primary: Continued Abstinence Rate**
  - **until end of active treatment (3-6 months) +**
  - **until end of study (at 12-15 months, db withdrawal in responders)**
- **Secondary:**
  - **Time to relapse (first drink)**
  - **% completers, time to withdrawal**
  - **Change in number of abstinent days**

Endpoints for Harm Reduction

- **No need for detox at inclusion (Active drinker at baseline!)**

- **Co-Primary:**

  Change to baseline in reduction of

  – **Total alcohol consumption TAC /month [g/day]**
  – **Number of HDD/month (HDD > 60g, resp. >40g/d)**

- **Secondary:**

  Responder analysis

  - **Proportion of patients with 50, 70, 90 % reduction in TAC**
  - **Proportion (30, 50, 70%) of patients with**
    – **DRL rightward shift (RS-DRL) or**
    – **Reaching low DRL (RL-DRL) etc. ….**

A clinically relevant difference to placebo should be shown

Nalmefene: first approved harm reduction drug

- Two 24-wk MTP pc, db studies (014: n=579, 023: n=655; ESENSE 1 / 2)
- Patients with AD acc. to DSM-IV-TR
- Mean baseline values
  - ADS 13.6
  - 78% with high / very high DRL
  - 19.3 HDD with 87.7 g alcohol/day TAC
- Treatments: NMF or placebo PRN as adjunct to BRENDA

Nalmefene: pre-random reduction in AC

- High rate of pre-random reduction in AC (18 resp. 33%)

- High rate of study discontinuation, partly differential

  014: 50 resp. 32%
  023: 30 resp. 28%

- Imputation of missing values of critical importance
  - BOCF, LOCF
  - MMRM (mixed model)
  - PMI (placebo means of first month MTP)
  - MI (multiple imputation of placebo at random ~ covariates)

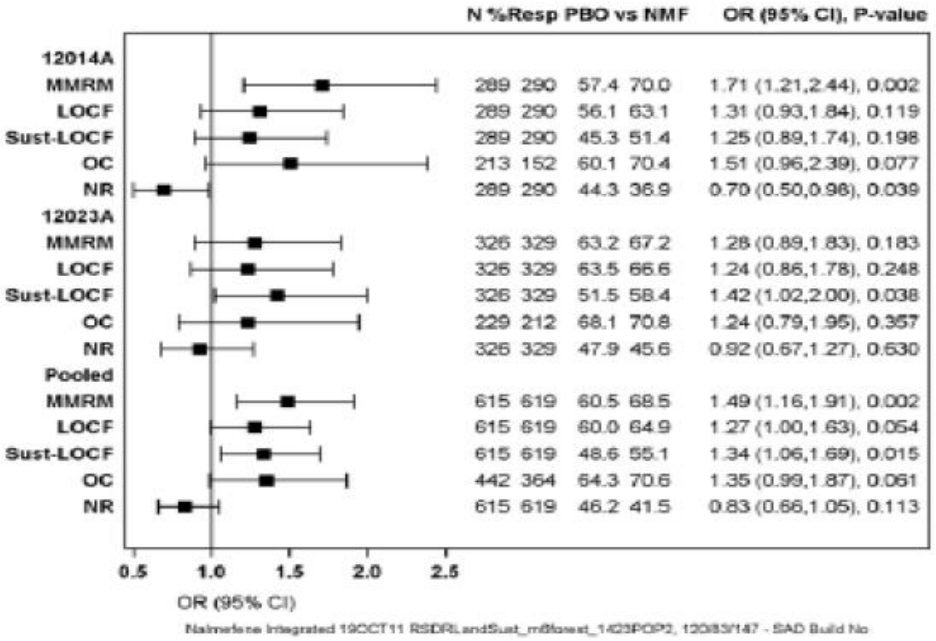
Results co-primary endpoints (MMRM) in patients with H/VH-DRL at randomization

- Overall Tx effect HDD
  - baseline 22.6/month
  - reduction by 10-11 HDD
  - net over placebo: -3.7 resp. -2.7

- Overall Tx effect TAC
  - baseline 105.5 g/day
  - reduction by 58-79 g/day
  - net over placebo: -18.3 resp. -10.3

Two-category rightward shift in DRL (RSDRL)

Panel 79 Key Secondary Analysis (RSDRL) – Proportion of Responders (%) and Odds Ratio for Response at Month 6 (FAS, LREG) – Studies 12014A, 12023A, and Studies 12014A and 12023A *Pooled*



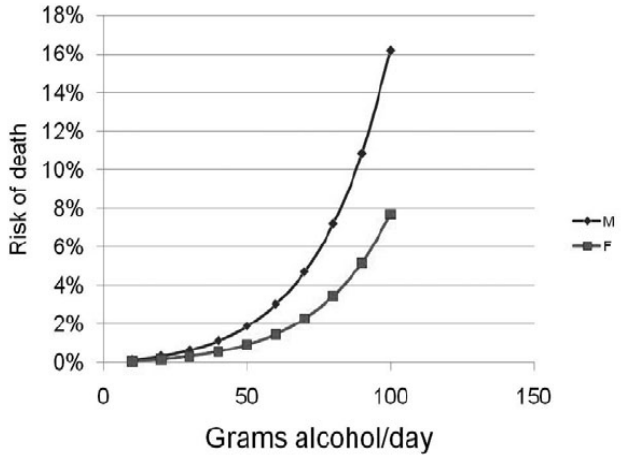
MMRM = missing values imputed using MMRM-predicted TAC

NR = missing values imputed as non-response

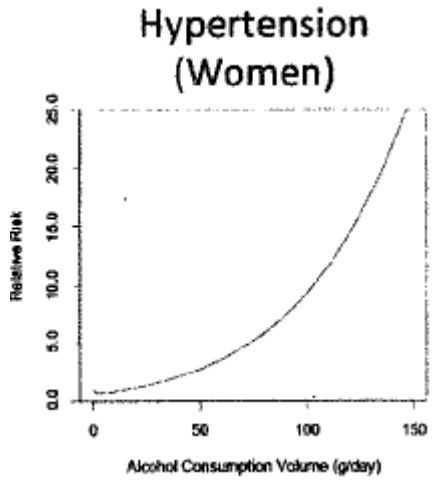
European Public AR, EMA/CHMP/748794/2012, 13 December 2012

Clinical relevance – reference to epidemiological TAC data

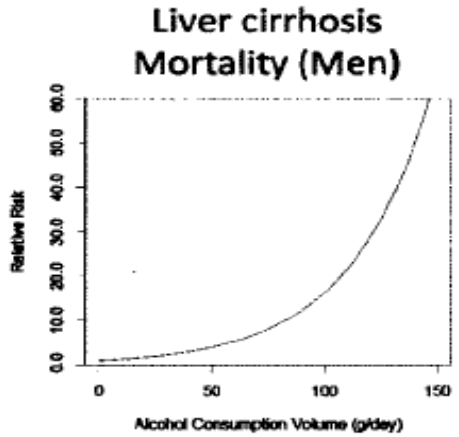
a)



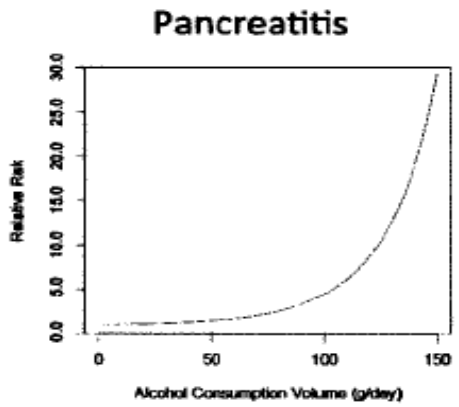
b)



c)



d)



a) Rehm J, Zatonski W, Taylor B, Anderson P. Addiction 2011; 106 (Suppl 1): 11-19
b-d) Shield KD, Parry C, Rehm J. Alc Res Curr Rev 2013; 35(2): 155-173

Regulatory perspective: endpoints

Various sensitivity analyses provided a range of significant resp. non-significant results

Similar pattern of range observed across continuous and dichotomized endpoints

- **Co-Primary:**

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Regulatory perspective: latest critique

Weak evidence on nalmefene creates dilemmas for clinicians and poses questions for regulators and researchers

Niamh Fitzgerald[1], Kathryn Angus[1], Andrew Elders[2], Marisa de Andrade[3], Duncan Raistrick[4], Nick Heather[5] and Jim McCambridge[6]

Addiction 2016; 111:1477-1487

Authors‘ view not fully shared by the EMA

http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2016/07/WC500211429.pdf

- No active comparator at hand in terms of harm reduction
- Keep actual drug label in mind
- Accurate delineation of target population plus

  Critical role of pre-random drinking levels

Look at moderators of drugs‘ effect

Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful?

Natalya C. Maisel[1], Janet C. Blodgett[1], Paula L. Wilbourne[1], Keith Humphreys[1,2] & John W. Finney[1,2]

Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), Menlo Park, CA, USA[1] and Department of Psychiatry and Behavioral Sciences, Stanford University Stanford School of Medicine, Stanford, CA, USA[2]

Addiction 2012; 108:275-293

Regulatory perspective: „Substitution therapy“

EMA Guideline clearly specifies

Addiction potential

Reinforcing/addiction potential of the test drug should be assessed to rule out switch of addiction

BfArM view:

New drug candidates with inherent addictive properties cannot refer to the current EMA guideline

Sponsors are invited...



…to contact regulatory authorities at an early stage for Scientific Advice



Comments? Protest?

Questions?

Thank you anyway!!

Back-up

DRL definition WHO

Table 2.2.3: Relative Risks for All-cause mortality for different average daily intakes of alcohol (from English *et al*, 1995)

Sex	Average daily intake							
	None	0.1-9g	10-19g	20-29g	30-39g	40-49g	50-59g	60+g
Male RR	1.00	0.88	0.84	0.93	1.01	1.06	1.20	1.37
(95% CI)		(0.86-0.90)	(0.82-0.86)	(0.91-.095)	(0.98-1.04)	(1.03-1.10)	(1.15-1.26)	(1.33-1.40)
Female RR	1.00	0.88	0.94	1.13	1.33	1.47	1.47	1.58
(95% CI)		(0.86-0.90)	(0.93-0.96)	(1.10-1.16)	(1.27-1.39)	(1.39-1.56)	(1.33-62)	(1.49-1.69)

WHO Guide for Monitoring Alcohol Consumption and Related Harm, 2000

Finally approved nalmefene indication

Selincro is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (see section 5.1), without physical withdrawal symptoms and who do not require immediate detoxification.

Selincro should only be prescribed in conjunction with continuous psychosocial support focussed on treatment adherence and reducing alcohol consumption.

Selincro should be initiated only in patients who continue to have a high drinking risk level two weeks after initial assessment.

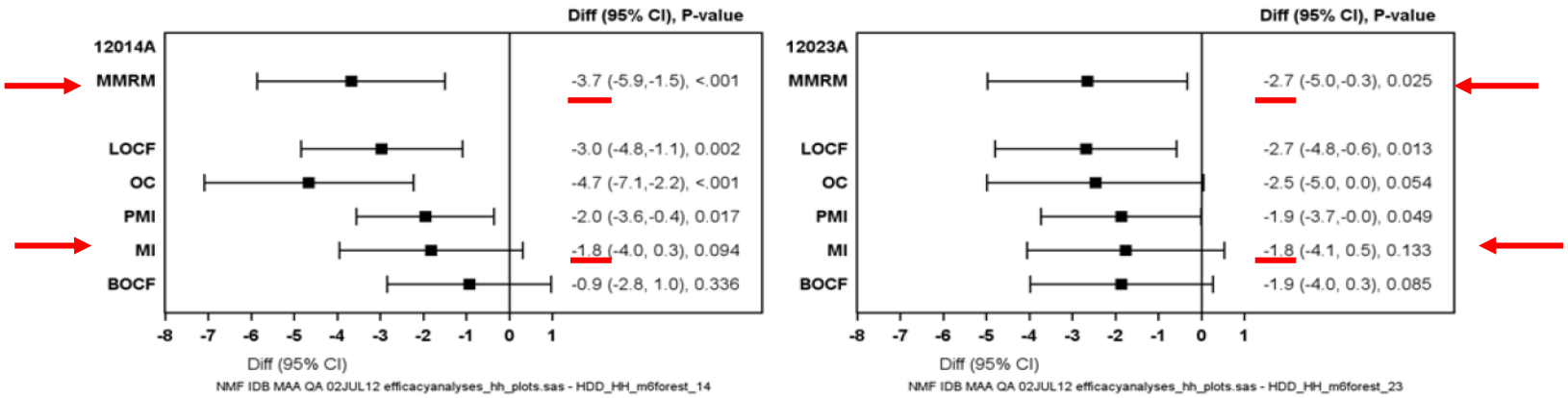
Current naltrexone indication

For use within a comprehensive alcoholism treatment program, with the aim of reducing the risk of relapse, maintaining abstinence, and reducing the desire for alcohol during the initial phases of recovery.

(e.g. Nemexin®, Nalorex®)

Results co-primary endpoints (H/VH-DRL, MMRM, MI)

Panel 93 Sensitivity Analyses – Changes from Baseline to Month 6 in HDDs (days/month) (FAS) – Patients with a *High* or *Very High* DRL at Baseline and Randomisation – Studies 12014A and 12023A



MMRM is the co-primary efficacy analysis and is included for comparison.
Negative values indicate a greater reduction in the number of HDDs and TAC in the nalmefene group than in the placebo group.

Overall Tx effect HDD
baseline 22.6/month
reduction by 10-11 HDD
net over placebo: -3.7 resp. -2.7

Overall Tx effect TAC
baseline 105.5 g/day
reduction by 58-70 g/day
net over placebo: -18.3 resp. -10.3

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European Public AR, EMA/CHMP/748794/2012, 13 December 2012