How to implement the recently released EMA guideline on "First-in-Human" trials ?

Academic Clinical Investigation Centers' Perspective

Pr D. DEPLANQUE

National Coordinator of the French Clinical Investigation Centers Network - Inserm,

Head of Clinical Investigation Center - CIC 1403 Inserm

Head of Clinical Research at Lille University Hospital

Department of medical Pharmacology – Inserm U1171 Degenerative and Vascular Cognitive disorders

Disclosure 2013-2017

Expertise, conferences, trip, royalties: Bayer, Biocodex, BMS, Pfizer, PMI

Clinical Investigator for clinical trials at CIC 1403 (most of Drug and Medical Devices companies)

Université de Lille 2 Droit et Santé

Centre Hospitalier Régional Universitaire de Lille

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

Faculté de Médecine Université Lille 2 Henri Warembourg

Scope of the July 2017 EMA guideline

- All new chemical and biological investigational medicinal products
- Advanced therapy medicinal products are not concerned but the present principles may be relevant
- The scope is not only FIH but also early clinical trials, namely studies which generate initial knowledge in humans on tolerability, safety, Pharmacokinetic and Pharmacodynamic…
- This may include collection of data on food/drug or drug/drug interactions, different age/gender groups, proof of concept, and bioavailability…
- This may be applied in both healthy volunteers and patients

General considerations

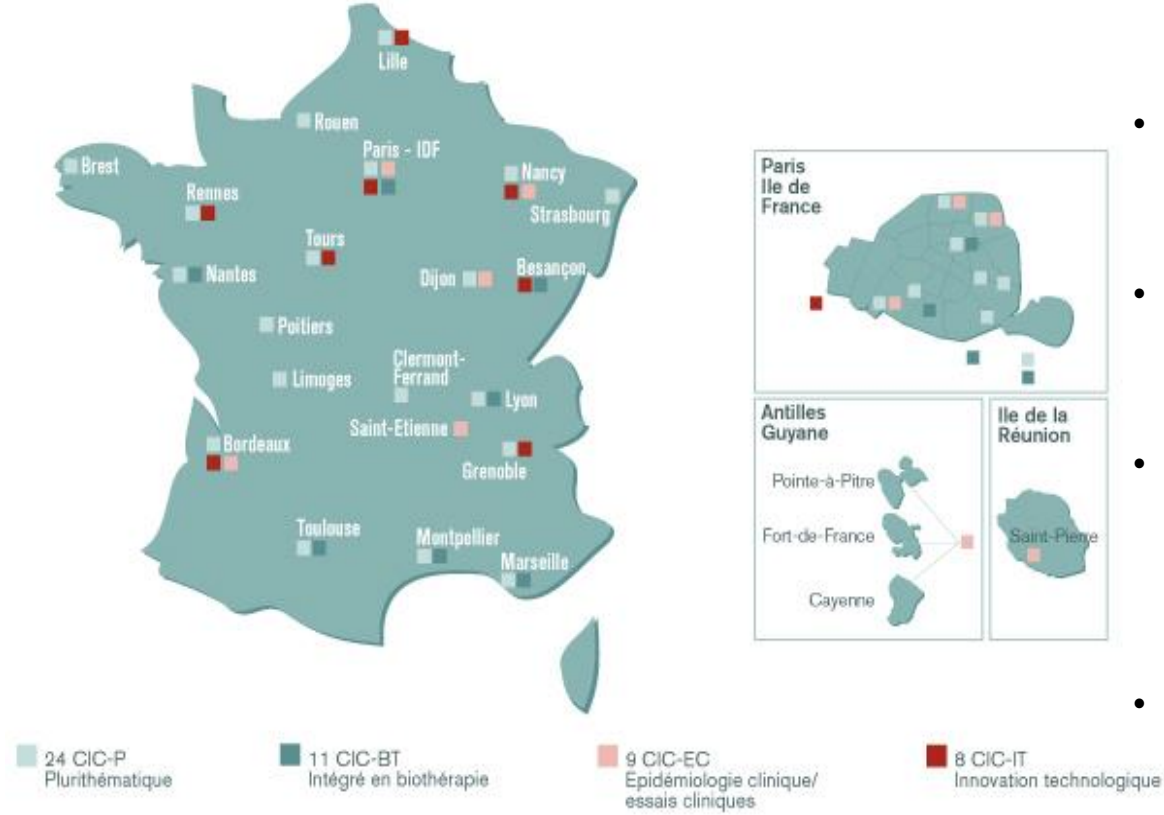
Based on uncertainty, risk mitigation strategies include:

- Ensuring adequate quality of the IMP
- Conducting additional non-clinical testing to obtain relevant data (animal models or human-derived material)
- Applying scientific rationale in the selection of the starting dose, dose escalation scheme and when defining maximum exposure
- Applying appropriate risk mitigating measures in the design and conduct of studies

Clinical Investigation Centers - Inserm

A total of 36 structures distributed on the whole French territory with different modules according to some specificities

(Multi-thematic activities, Epidemiology, Biotherapy, Technology innovation…)



- Partnership between Ministry of Health and INSERM
- Fully integrated to University hospital with a privileged access to patients
- Activities from Translational and Proof of concept Researches to Phase III or Cohort studies…
- With both public and private sponsors

Most of these structures have an authorization for FIH / early clinical trials but only a limited number of beds

Regarding EMA recommendations what could impact Academic Centers activities?

- Choice of study population and protocol overall design
- Starting dose, maximum dose and exposure duration
- Half life or PK/PD issues
- Number of subject by cohort
- Sequence and interval between dosing in a same cohort
- Dose escalation increments
- Transition to next dose increment cohort or next study part
- Stopping rules
- Safety parameters to monitor
- Trial sites
- Inclusion of a placebo arm…

Nevertheless it would have low impact…

- Early-phase trials developed in Academic Clinical Investigation Centers are not strictly comparable to early-phase trials conducted in other Phase 1 Centers
- Some EMA recommendations are largely applied in Academic Clinical Investigation Centers for a long time

FIH/early phase trials in Academic Centers?

- **What is not done?**
  - FIH with molecules of low therapeutic interest or with molecules sometimes considered as "Me-Too"
  - Studies about Food/Drug or Drug/Drug interactions
  - FIH that should include an extremely important number of subjects in an extremely short period…
- **What is done?**
  - FIH with molecules developed from academic research
  - FIH with molecules within public/private partnership
  - Proof of concept studies using already marketed drugs in healthy volunteers
  - Early phase trials in patients (not only in oncology)

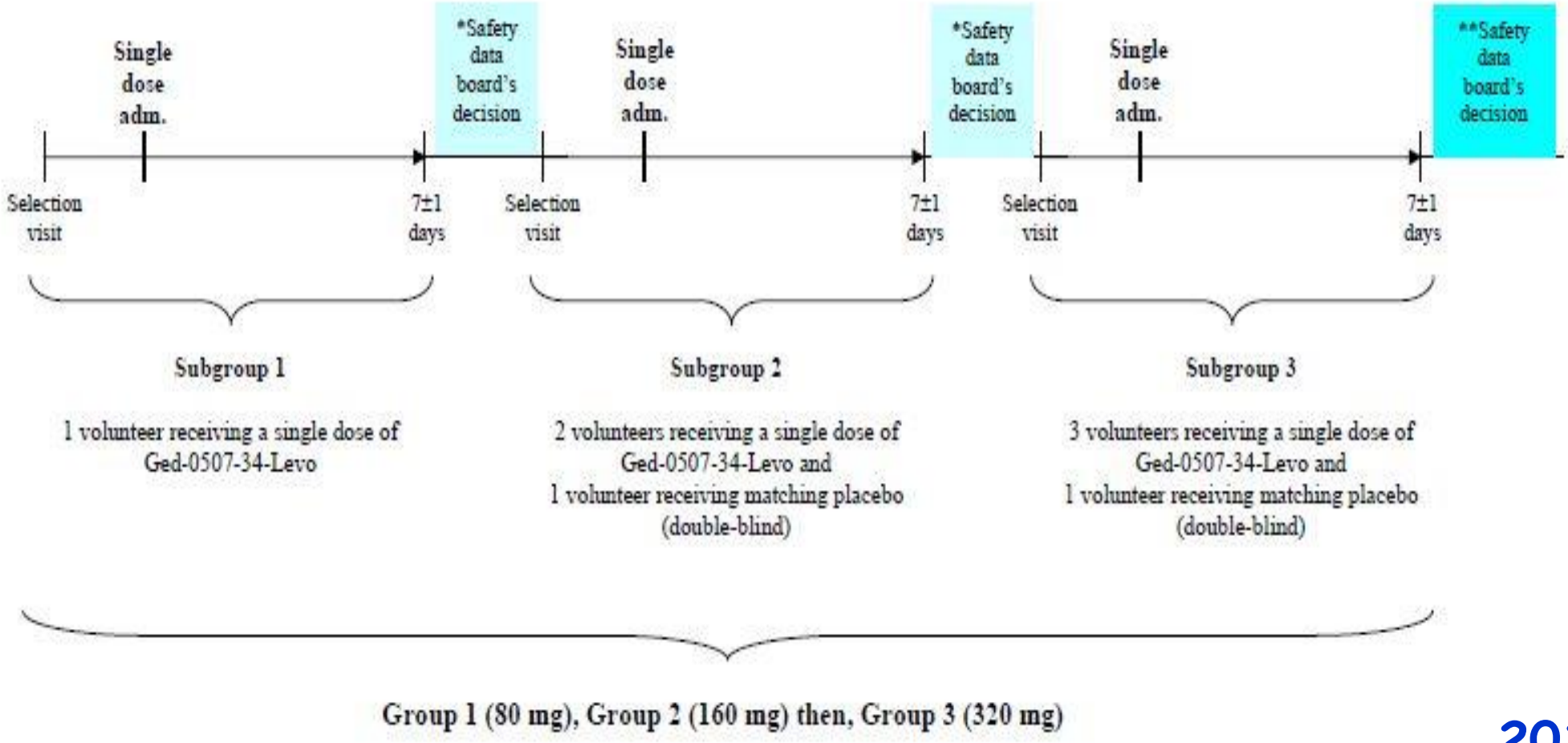
Multicenter approaches according to bed/patients number…

Some examples in collaboration with private companies...

- A FIH study including a placebo arm and a specific design to manage the changes of cohort
- An early-phase trial with autologous cell therapy including a specific procedure for long term safety evaluation and substantial protocol amendments regarding the number of administration
- A European public-private research program including several early-phase studies with both drugs and complex pharmacodynamic measures

FIH of GED-0507-34-Levo

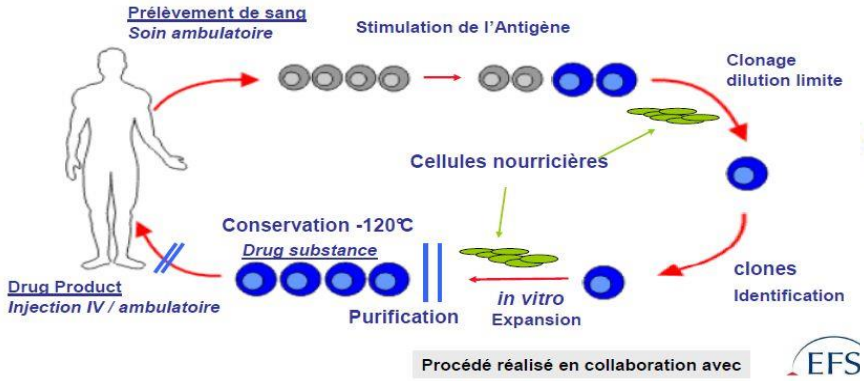
The tested drugs will be administered to healthy male volunteers beginning with the lowest-dose group, Group 1 (80 mg), and proceeding stepwise to the highest dose group, Group 3 (320 mg), subjects in each group being dosed and evaluated sequentially (three subgroups)

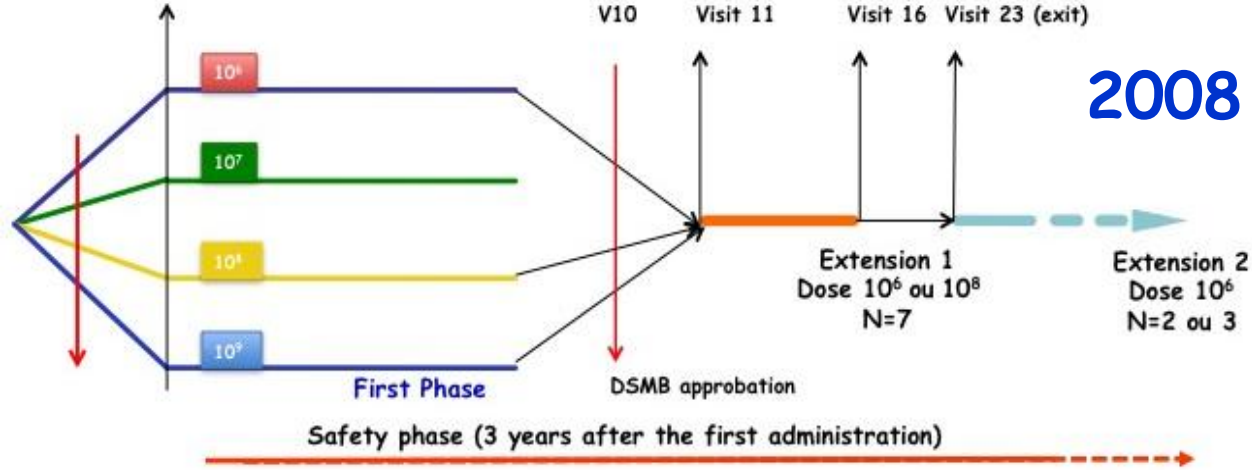


2010

Cell therapy for Crohn Diseases

Autologous cell therapy (Tr1 Lc)





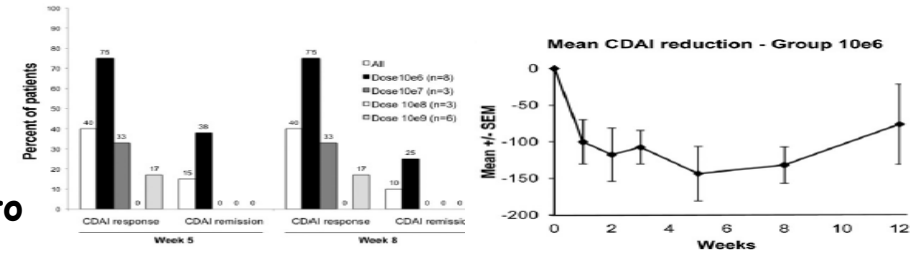
Study protocol

- **Design :** An open, non controlled, multicenter study (5 centers)
- **Population :** severely impaired Crohn patients (CDAI 220-450)
- **Objectives :**
  - ✧ **Primary :** safety and tolerance evaluation of autologous Tr1
  - ✧ **Secondary :**
    - Both clinical and biological effects
    - Determination of the dose with acceptable benefit/risk
- **Follow-up:** 3 months (safety data during 12 months)
- **Doses:** 4 cohorts 10^6,10^7,10^8 et 10^9 cells (single-injection)
- **DSMB:** evaluation of safety data of each cohort by taking into account a period of at least 3 weeks

Two extensions authorized

-1st extension (7 visits during 13 weeks) to better evaluate security and tolerance of a second administration

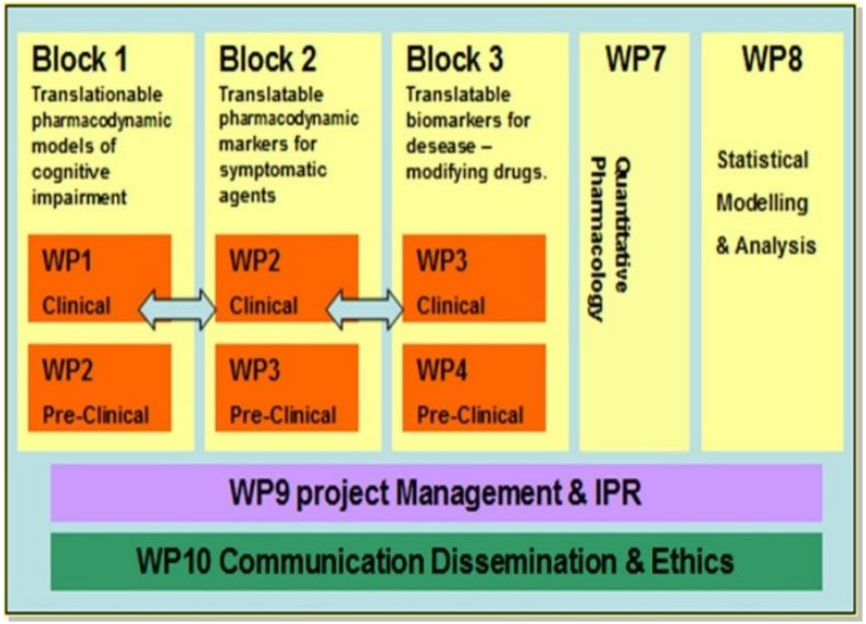
-2d extension (2 visits by cycle of 2 months): realized after a demand from both patients and investigators to provide an access to multiple injection of the product

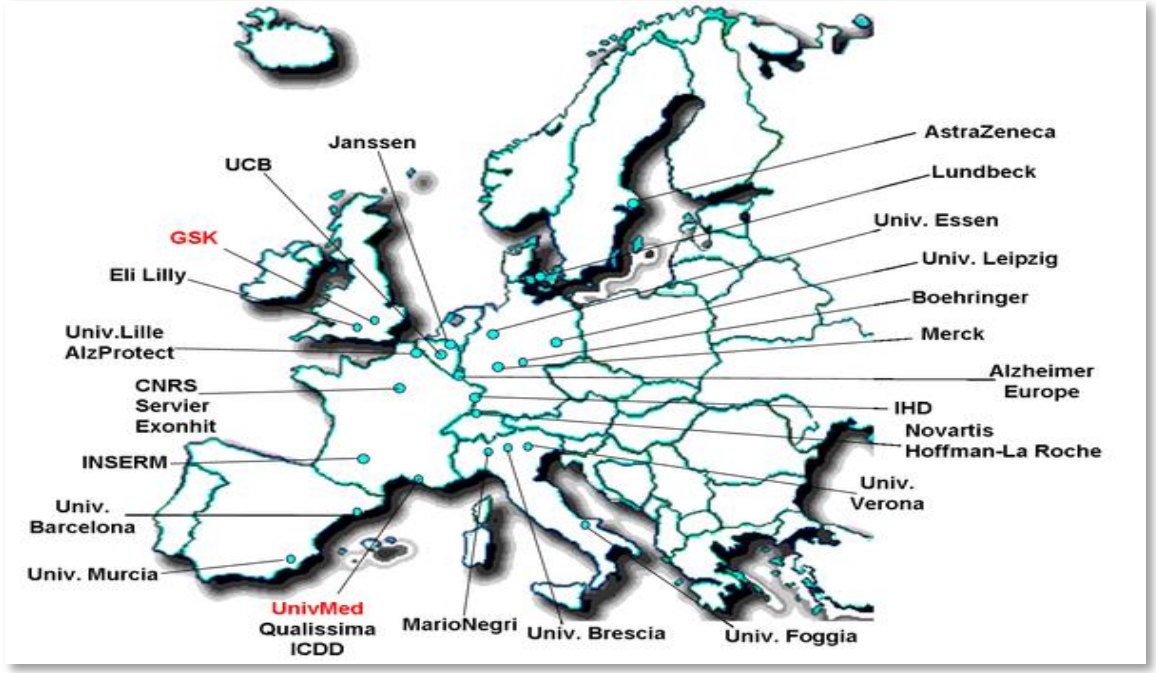


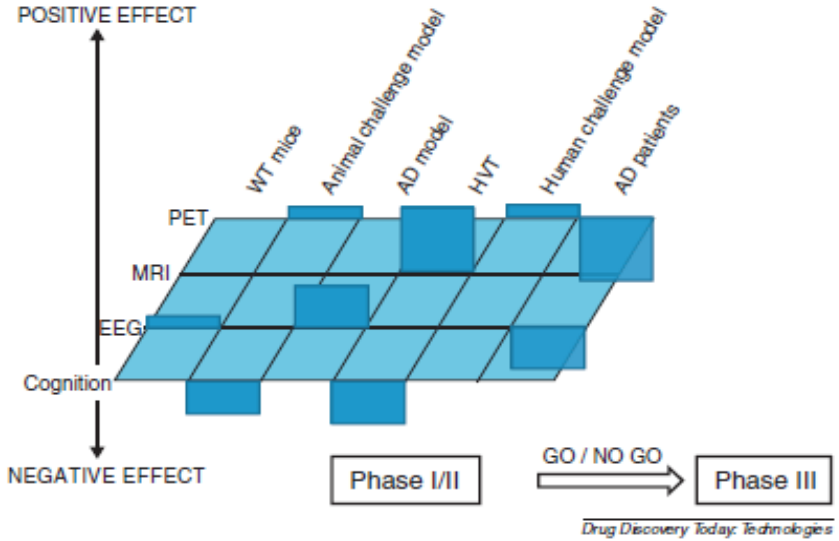
Desreumaux et al, *Gastroenterology* 2012

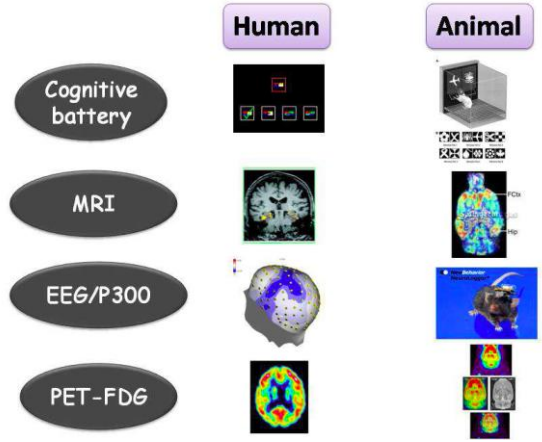
Pharmacog: an IMI European Project

To develop platforms to evaluate cognitive and brain functions in both animal and humans
To show that new biomarkers may be used to early determine drug pharmacodynamic profile









Coordination: Pr Bordet, U1171 Inserm

Pharmacog – Clinical approaches

Donepezil
Memantine

Patients

Healthy volunteers

Cantab cognition

Electrophysiology

- Rest EEG & synchronisation
- ERP (P300)
- Vigilance

Brain imaging

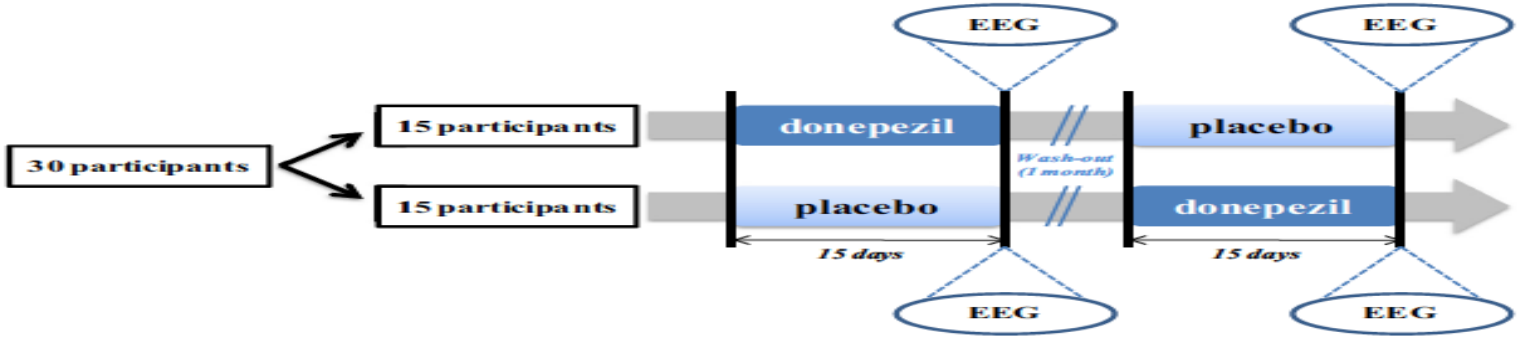
- MRI (morphometric, functional)
- PET FDG and other ligands

Virtual environment

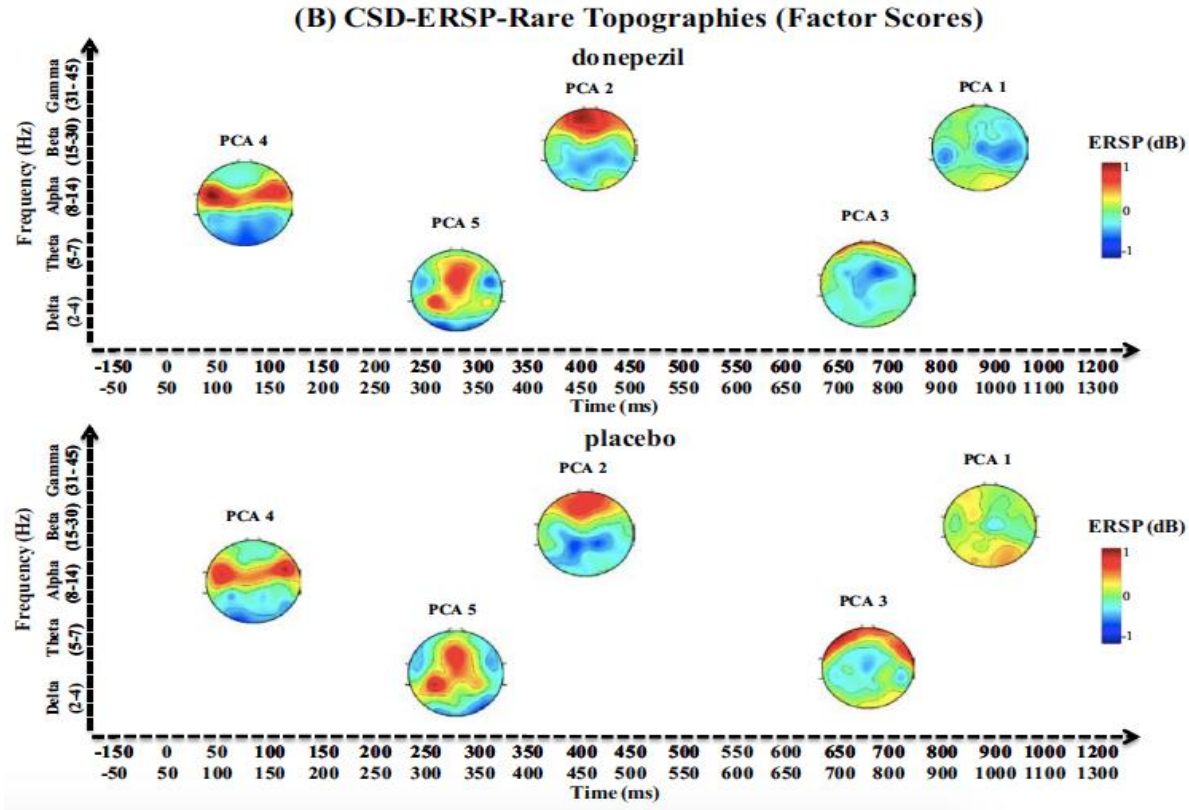
Challenge tests

- None
- Sleep deprivation
- Hypoxia

EEG: a tool to evaluate subtle brain changes



- Time–frequency analyses were used to identify dynamic electroencephalographic markers of donepezil's effect in healthy young adults.
- Inter-trial coherence and event-related spectral perturbation analyses can detect subtle changes related to donepezil's effects.
- Electroencephalography may be a valuable tool for predicting the efficacy of drug candidates prior to Phase II/III clinical trials in Alzheimer's disease.



Leroy et al. *Clin Neurophysiol* 2016

Conclusion

- For Academic Centers, the present EMA guideline validates some approaches developed for a long time
- A specific attention should be given to the management of multicenter studies
- The present guideline does not resolved the French issues resulting from 2016 accident:
  - Increased reluctance to participate in early phase studies
  - New modalities of unwanted events' declaration