Direct double-blind analysis arguing for a synergistic therapeutic effect of a fixed low-dose combination of acamprosate and baclofen in patients with AD

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**Background**

PXT-864 is a fixed low-dose combination of baclofen (GABA_B receptor agonist) and acamprosate (glutamatergic modulator) deduced from a network pharmacology-based approach that systemizes the identification of new synergistic combinations of repurposed drugs.

It has shown multiple reversions of pathological alteration in cellular and animal models of AD (Chumakov et al, 2014) in addition to good safety and preliminary evidence of efficacy in early clinical phases (results presented at CTAD 2014, 2016 and 2017 - cf poster 40).

If the synergistic profile of PXT-864 in preclinical studies has been clearly established, it remains still not shown in human as no trial with factorial design was performed (comparing the two single drug arms to the drug combination arm).

Here we show strong evidence of a synergistic therapeutic effect of PXT-864 in a phase II clinical trial (NCT02361424 and NCT02361242) on various endpoints including ADAS-Cog and MMSE.

Given that subjects were treated with the combination only, we used an innovative approach based on the blood concentrations of the single drugs and hence is double-blind. Our results provide a major proof-of-action of PXT-864 in AD while our approach could become a key methodology for the development of drug combinations.

**Study protocol**

- 45 patients with anti-dementia treatment naive mild AD (MMSE 20-26).
- 31 patients on Per Protocol population for PK analysis ($C_{max}$ blood concentration).
- Multicenter, prospective, single-blind, explorative study.
- 3 months duration under challenge/re-challenge/re-challenge, each period consisting of 4 weeks, PXT-864, placebo, and PXT-864. Thereafter, patients entered the extension phase for another 24 weeks of PXT-864.
- 3 doses tested (formulation: oral given twice daily).
  - PXT-864 Dose 1 = 0.8 mg acamprosate + 12 mg baclofen
  - PXT-864 Dose 2 = 2 mg acamprosate + 30 mg baclofen
  - PXT-864 Dose 3 = 40 mg acamprosate + 24 mg baclofen
- 6 months follow-up with possibility of donepezil co-administration from week 24 (physician decision).
- Various endpoints measured at each visit and PK at H2 post dose ($C_{max}$).

**Synergy / Additivity**

- Synergy between drugs A and B is declared when effect of the combination (A + B) exceeds the simple addition of each drug effect.
- It usually requires comparing the single drugs' effects (A or B) to the combination effect (A + B) (Foucquier et al, 2015).
- In the absence of single drug groups, we suggest that a measurement of single drug concentrations in body fluids (such as blood and as measured during PK analysis) after administration of the combination (A + B) only could be used as A and B blood concentrations.
  - Strongly vary from individual to individual.
  - But with no strong correlation.
- By applying a threshold on the concentration of drug A and another on the concentration of drug B, we can define 4 groups by low (A_L or B_L) and high (A_H or B_H) blood concentrations.
- Therapeutic effect is calculated for each group then synergy is assessed by using the Bliss method (Foucquier et al, 2015):

  $$ Cl_{add} = 0$$

  Combination Index by Bliss ($Cl_{add}$) < 1 means synergy

  Thresholds for A and B are then shifted in order to detect concentrations with the optimal synergistic effect.

**Results**

**Conclusions**

1. **Preliminary** data in human from our phase 2a AD study
   - Done only at 3 months on ADAS-Cog and MMSE (we now check them at each visit as well as additional endpoints).
   - Sample size is not optimized for this new approach.
   - Measure of concentration at $C_{max}$ for both drugs.
2. This method allows a double-blind assessment of synergy / additivity = superiority of the combo versus single drugs (requirement of FDA).
3. It would provide a strong proof of concept of our general approach.
4. It would optimize further development based on personalized dosage optimization to significantly enhance responder rate.