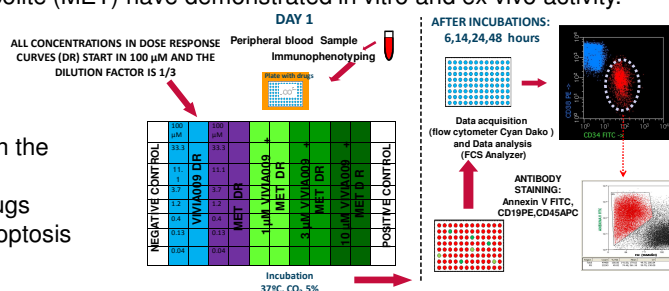


INTRODUCTION

- ★ Vivia009 is a patented new drug indication for B-cell chronic lymphocytic leukemia (B-CLL), a cancer of white blood cells that originates in bone marrow and develops in lymph nodes.
- ★ Both, Vivia009 and its metabolite (MET) have demonstrated in vitro and ex vivo activity.

METHODS

- ★ Blood samples from 13 patients diagnosed with B-CLL were received in the lab within 24 hours post-extraction.
- ★ Blood was seeded in plates with drugs and after a certain incubation time, apoptosis was measured with a flow cytometer.



OBJECTIVES

- ★ To develop a pharmacodynamic model describing the apoptotic effects of the two compounds separate and in combination characterizing possible types of interactions: additive, antagonistic, or synergistic.

VIVIA009

MODEL DEVELOPMENT

METABOLITE

1st → Apoptotic Model of the leukemic cells in the absence of drug, Basal apoptosis (E_0):

$$E_0 = A_0 + \frac{(Emax_0 - E_0) \times Time^{\gamma_0}}{Time^{\gamma_0} + T_{50}^{\gamma_0}}$$

2nd → Model development for each drug separately; Initial drug concentration (C_p), Effective drug concentration (C_e):

Effect Compartment Model + Hill Equation

$$\frac{d[C_p]}{dt} = 0$$

$$\frac{d[C_e]}{dt} = Ke_0 \times [C_p - C_e]$$

$$\% Apop = E_0 + \frac{(100 - E_0) \times C_e^{\gamma}}{C_e^{\gamma} + EC_{50}^{\gamma}}$$

3rd → The synergism model [3]:

$$\% Apop = Emax \times \frac{\left(\frac{C_A}{EC_{50A}} + \frac{C_B}{EC_{50B}} + \alpha \times \frac{C_A}{EC_{50A}} \times \frac{C_B}{EC_{50B}} \right)^{\gamma}}{\left(\frac{C_A}{EC_{50A}} + \frac{C_B}{EC_{50B}} + \alpha \times \frac{C_A}{EC_{50A}} \times \frac{C_B}{EC_{50B}} \right)^{\gamma} + 1}$$

③ $\alpha < 0 \rightarrow$ antagonistic
 $\alpha = 0 \rightarrow$ additive
 $\alpha > 0 \rightarrow$ synergistic

$$\gamma = \gamma_B \times \frac{\frac{C_B}{EC_{50B}}}{\frac{C_A}{EC_{50A}} + \frac{C_B}{EC_{50B}}} + \gamma_A \times \left(1 - \frac{\frac{C_B}{EC_{50B}}}{\frac{C_A}{EC_{50A}} + \frac{C_B}{EC_{50B}}} \right)$$

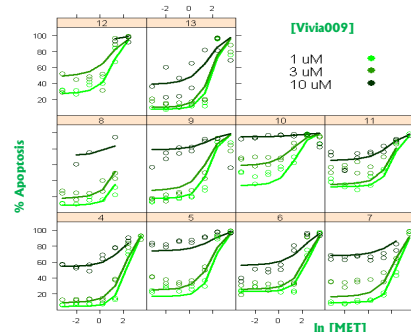


Figure 5.- Individual Model Predictions (lines) and observations (dots) vs. In of MET concentration for 14 hours incubation with increasing concentration of Vivia009

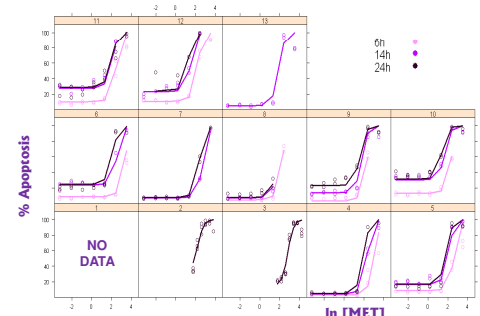


Figure 2.- Individual Model Predictions (lines) and Raw Data (dots) of the effect vs. In of Metabolite concentration

	Typical Estimate	IIV (%)	η - ϵ - Shrinkage (%)
EC_{50B} (μ M)	4.43 (15.4)	43.8 (43.9)	1.7
γ_B	3.3 (11.2)	--	--
KE_{0B} (h^{-1})	0.055 (33.1)	78.5 (45.2)	10
$Emax_0$ (%)	15.3 (27.9)	95.8 (52)	2.3
T_{50} (hr)	10.4 (20.3)	51.7 (41.8)	1
γ_0	4.65 (21)	--	--
A_0 (%)	3 (43)	--	--
Residual error (%)	2.2 ± 15.2		2.14

Table 2.- System and pharmacodynamic parameters for MET EC_{50B} : drug concentration eliciting half of the maximum effect; γ_B : slope of MET effect; KE_{0B} : parameter controlling the delay of the apoptotic signal; T_{50} : time necessary for eliciting half of the maximum basal effect ($Emax_0$); γ_0 : slope basal effect

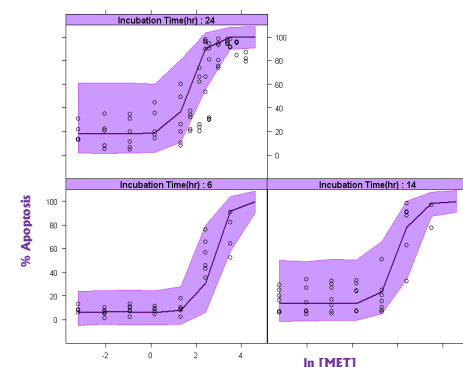


Figure 4.- Visual Predictive Check corresponding to: 5th and 95th percentiles (violet area), model mean (line) and observations (dots)

CONCLUSIONS

REFERENCES

- ★ Vivia009 and its metabolite showed similar potencies and mean apoptotic signal transduction times.
- ★ The interaction parameter (α) was estimated with a value very similar to 0 (-8.9×10^{-3}) indicating additive effects between Vivia009 and its main metabolite.
- ★ Modeling results are supported by literature data; the mechanism of action of Vivia009 and its metabolite seems to be through the mitochondrial signalling pathway, producing segregation of proapoptotic proteins. Both acting on the same pathway.

- [1] Moreno D, J Pharm Pharmacol. 2008 Jan;60(1):77-82.
- [2] Minto CF, Anesthesiology. 2000 Jun;92(6):1603-16.
- [3] Kern SE, Anesthesiology. 2004 Jun;100(6):1373-81.