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INTRODUCTION

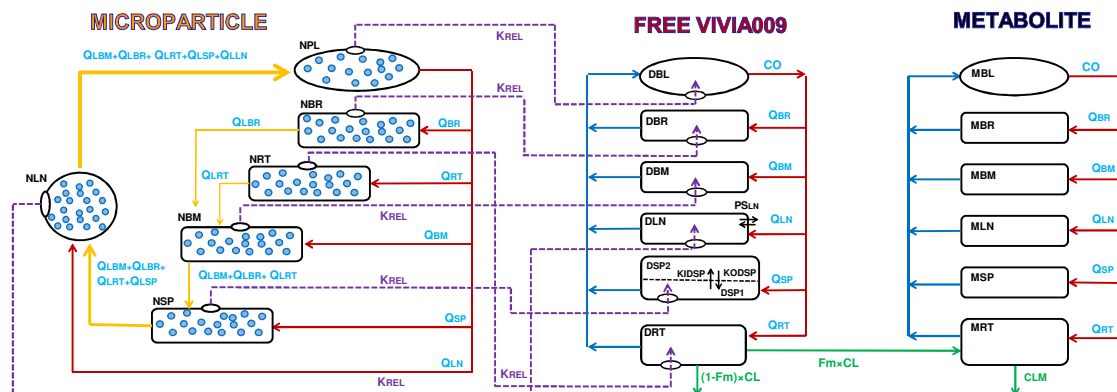
- ★ Vivia009 is a patented new drug indication that targets B cell population overproliferation in Non-Hodgkins lymphoma.
- ★ In order to prevent side effects and to increase drug efficacy, a new delivery system (microparticle) has been developed and its pharmacokinetic properties are currently being studied.

OBJECTIVES

To develop an integrated physiological based pharmacokinetic model (PBPK) capable to describe simultaneously the biodistribution of the parent drug and its main metabolite, after iv administration of either Vivia009 free or encapsulated.

SELECTED MODEL

Figure 2.- PBPK model for microparticle (all) or free drug (middle & right part). The organs responsible for drug efficacy and side-effects are represented by a rectangular compartment and connected in an anatomical manner with blood flow (red, blue) and lymphatic flow (yellow). Compartments are named as follows: the first letter N, D, M represent microparticle, free drug and metabolite respectively. The second and third letter define the organ, PL, BR, BM, LN, SP, RT, stand for plasma, brain, bone marrow, lymph node, spleen and rest of tissues respectively. In vivo release of Vivia009 from the microparticle is represented by KREL.



MODEL EQUATIONS & PREDICTIONS: on the left is the microparticle diagram, with its equations underneath, and its model predictions. The middle panel corresponds to the free drug and the right one to the metabolite. The microparticle is bound to the free drug model through the in vivo release constant (KREL). The free drug is bound to the metabolite model through the hepatic clearance (Fm×CL). Parameter estimates of the models can be found on Table 3. Due to the fast in vitro release profile of the microparticle (data not shown), at the injection time, part of its dose had been already released (F1). Mass balance for some of the compartments are shown below:

$$\frac{d(NPL)}{dt} = (Q_{LRT} + Q_{LBM} + Q_{LBR} + Q_{LSP} + Q_{LLN}) \times \frac{C_{NPL}}{K_{PNL}} - (Q_{BR} + Q_{BM} + Q_{SP} + Q_{RT} + Q_{LN}) \times C_{NPL} - K_{REL} \times NPL$$

$$\frac{d(NLN)}{dt} = Q_{LN} \times C_{NPL} + (Q_{LSP} + Q_{LBM} + Q_{LBR} + Q_{LRT}) \times \frac{C_{NPL}}{K_{PNL}} - (Q_{LLN} + Q_{LSP} + Q_{LBM} + Q_{LBR} + Q_{LRT}) \times \frac{C_{NPL}}{K_{PNL}} - K_{REL} \times NLN$$

$$\frac{d(NSP)}{dt} = Q_{SP} \times C_{NPL} + (Q_{LBM} + Q_{LBR} + Q_{LRT}) \times \frac{C_{NPL}}{K_{PNL}} - (Q_{LSP} + Q_{LBM} + Q_{LBR} + Q_{LRT}) \times \frac{C_{NPL}}{K_{PNL}} - K_{REL} \times NSP$$

$$\frac{d(DLN)}{dt} = PS_{DLN} \times (Q_{LN} \times C_{DBL} - Q_{LN} \times \frac{C_{DLN}}{K_{PDN}}) + K_{REL} \times NLN$$

$$\frac{d(DSP1)}{dt} = Q_{SP} \times C_{DBL} - Q_{SP} \times \frac{C_{DSP1}}{K_{PDSP}} - KIDSP \times DSP1 + KODSP \times DSP2 + K_{REL} \times NSP$$

$$\frac{d(DSP2)}{dt} = KIDSP \times DSP1 - KODSP \times DSP2$$

$$\frac{d(DRT)}{dt} = Q_{RT} \times C_{DBL} - Q_{RT} \times \frac{C_{DRT}}{K_{PDRT}} - (F_m \times CL - CLM) \times \frac{C_{DRT}}{K_{PDRT}} + K_{REL} \times NRT$$

$$\frac{d(MPL)}{dt} = Q_{BR} \times \frac{C_{MBR}}{K_{PMBR}} + Q_{BM} \times \frac{C_{MBM}}{K_{PMBM}} + Q_{LN} \times \frac{C_{MLN}}{K_{PMLN}} + Q_{SP} \times \frac{C_{MSP}}{K_{PMSP}} + Q_{RT} \times \frac{C_{MRT}}{K_{PMRT}} - Q_{T} \times C_{MBL}$$

$$\frac{d(MRT)}{dt} = Q_{RT} \times C_{MBL} + F_m \times CL \times \frac{C_{DRT}}{K_{PDRT}} - (Q_{RT} + CLM) \times \frac{C_{MRT}}{K_{PMRT}}$$

$$\frac{d(MSP)}{dt} = Q_{SP} \times C_{MBL} - Q_{SP} \times \frac{C_{MSP}}{K_{PMSP}}$$

Table 3.- Estimated parameter values for the microparticle (yellow), free drug (violet) and metabolite (black). Kp, partition coefficient; PS, permeability surface factor; KI & KO, slowly interacting tissue pool's constants. Parameters in blue are the new microparticle estimates for free drug total clearance, metabolite clearance and fraction of parent's drug metabolised by the liver represented as CL, CLM and Fm respectively.

MICROPARTICLE MODEL PARAMETERS	FREE 009 MODEL PARAMETERS	METABOLITE MODEL PARAMETERS
K _{PBR} = 4.47	K _{PBR} = 4.5	K _{PBR} = 16.3
K _{PBM} = 0.707	K _{PBM} = 0.392	K _{PBM} = 0.31
K _{PMLN} = 50.5	K _{PMLN} = 68.6	K _{PMLN} = 17.7
K _{PNSP} = 0.196	K _{PNSP} = 28.5	K _{PNSP} = 27.6
K _{PRT} = 0.84	K _{PRT} = 7.97	K _{PRT} = 1.18
F1 = 0.45	PS _{DLN} = 3.49	CLM = 0.0267 L/h
KREL = 0.0927	KIDSP = 32.9 h ⁻¹	Fm = 0.0593
CL = 0.537 L/h	KODSP = 9.6 h ⁻¹	
CLM = 0.9352 L/h	CL = 0.257 L/h	
Fm = 0.0811		

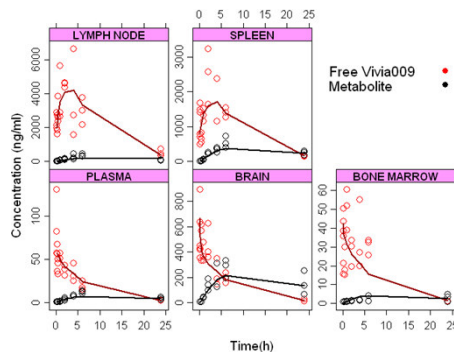
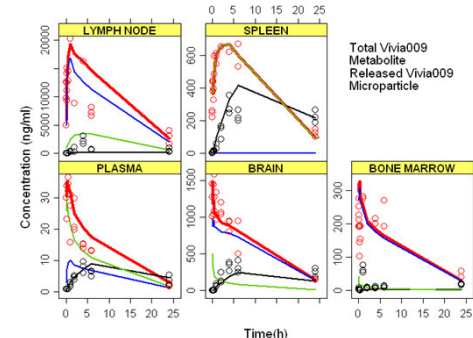


Figure 3.- Comparison of PBPK model predictions (lines) and observed concentrations (dots) of Vivia009 and its metabolite after administration of **MICROPARTICLES**. Total Vivia009 = Released Vivia009 + Microparticle

Figure 4.- Comparison of PBPK model predictions (lines) and observed concentrations (dots) of Vivia009 and its metabolite after administration of **FREE DRUG**.

CONCLUSIONS

- ★ Based on the results of the modeling exercise, 45% (F1) of the microparticles' dose was released before the bolus administration behaving as a free drug.
- ★ CL, CLM and Fm increased 2, 1.3 and 1.3 times respectively, when the drug was administered as a microparticle (Table 3).
- ★ Modelling results will be used to:
 - 1.- Scale to first dose in humans, free drug as well as microparticle.
 - 2.- Predict rat and human biodistributions of similar new delivery systems.

METHODS

Sprague Dawley rats (n=51) divided in 2 groups were treated with 0.75 mg/kg of either free drug or microparticles. 3 animals were sacrificed at each time point 0.08, 0.16, 0.25, 0.5, 1, 2, 4, 6 and 24 hours after iv bolus injection. Samples of plasma, axillary lymph node, brain, spleen and bone marrow were collected to measure Vivia009 and its metabolite concentrations.

Table 2.- Physiological parameters taken from the literature and additional information used to develop the PBPK models of Vivia009.

	Blood Flow = Q (L/h)	Lymph flow = Q _L (L/h)	Organ Volumes (L)
BRAIN	0.08 [2]	0.0032 [1]	0.0017 [2]
BONE MARROW	0.152 [2]	0.00608 [1]	0.0158 [2]
LYMPH NODE	0.0096 [3]	0.000384 [1]	0.0008 [5]
SPLEEN	0.037 [5]	0.00074 [1]	0.00053 [5]
PLASMA	Cardiac Output = 4.44 [4]	Q _L = 0.133 (3%)	0.0078 [4]
Rest (adipose, gut, heart, kidneys, liver, lungs, muscle, pancreas, skeleton, skin, stomach, testes, thymus)	CO-Q _{BR} -Q _{BM} -Q _{LN} -Q _{SP} [7]	Q _L = Q _L -Q _{LN} -Q _{SP} -Q _{LN} -Q _{SP}	0.207 [7]
PARTITION COEFFICIENTS	AUC _{tissue} = Kp AUC _{plasma} [6]		
BLOOD TO PLASMA RATIOS	VIVIA009 = 1.6 METABOLITE = 1.75 (experimentation)		

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