Increase in glucose as pharmacodynamic biomarker following administration of the PI3K/mTOR inhibitor LY3023414: quantitative description using modelling

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Background:

The phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway is disregulated in many malignant diseases. LY3023414 (LY) is an oral ATP competitive inhibitor of the class I PI3K isoforms, mTOR and DNA-PK currently investigated in patients with advanced solid tumors. PI3K signalling has a major role in insulin homeostasis, mainly via the activation of the AKT/PKB and the PKCζ cascades [1].

Objective:

To quantitatively describe the possible impact of LY3023414 on glucose homeostasis through modelling.

Data available and Method:

LY pharmacokinetics (PK), glucose (GL) and C-peptide (Cpep) data under fasting condition (predose and post LY administration – up to 4 hours) from first in man on-going dose escalation study were analyzed using non-linear mixed effect modelling (implemented in NONMEM (version VII)) (tables 1 and 2). Patients were allowed to eat a meal after the 4-hour postdose samples were collected, and therefore, after the 4-hour time point, GL and Cpep data do reflect not only the impact of LY but also the effect of the meal.
LY PK data were also analysed using classical non-compartmental analysis.

Table 1: Study design: Dose levels evaluated

LY3023414 assigned Dose mg	LY3023414 daily dose	# Patients
20 mg QD	20 mg	3
40 mg QD	40 mg	3
80 mg QD	80 mg	3
150 mg QD	150 mg	3
100 mg BID	200 mg	2
225 mg QD	225 mg	3
150 mg BID	300 mg	5
325 mg QD	325 mg	7*
200 mg BID	400 mg	55 enrollment on-going
450 mg QD	450 mg	3**
250 mg BID	500 mg	4

*Only 6 patients PK data taken into account because one outlier with very low concentration due to vomiting was excluded from analysis.
**Only 2 patients PK taken into account because clear DDI with clarythromycin for the third patient

Table 2: Concentration data, LY3023414, glucose & C-peptide

	# of patients	# of data point
LY3023414 (LY)	89	1192
Glucose (GL)	87	718
C-peptide (Cpep)	43	503

Results:

PK analyses showed a dose-proportional increase in LY exposures (AUC) (= constant clearance and normalized AUC with dose) up to 325 mg with a half-life of 1.9 h (CV% = 35%; n = 68; 90% CI 1.74–2.00 h; range 1.01–5.06 h) and a clearance of 74.3 L/h (CV% = 56%) (figures 1 and 3).

A two compartment model with first order absorption rate describes LY PK profile (figure 2, table 3). Graphical evaluation indicates LY leads to dose dependent increase in GL (hysteresis loop) (figures 4, 5, 6). Hence, LY impact on GL is described by an indirect response model with a sigmoidal EMAX relationship linking LY to GL input rate (figures 2, 5, 6 and table 4). A similar model describes the effect of GL on Cpep input rate (figures 2, 7 and table 4).

The model predicts the maximum increase in GL, 1.2 fold (1.13-1.25 90% CI) following 200 mg, at approximately 3 h post dose followed by a return to baseline GL value by approximately 8h (dosing interval of 12 h). This effect is lower than the reported maximum increase in GL (approximately 1.5 fold) following standard meal [2].

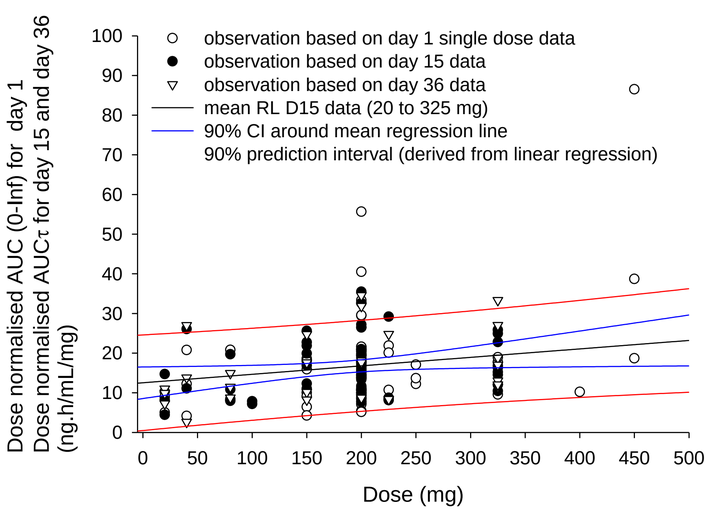


Figure 1: Dose-normalized LY3023414 AUC versus dose

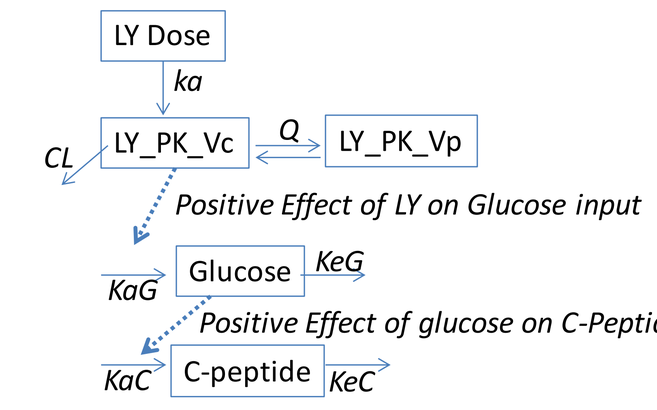


Figure 2: Model Schematic representation

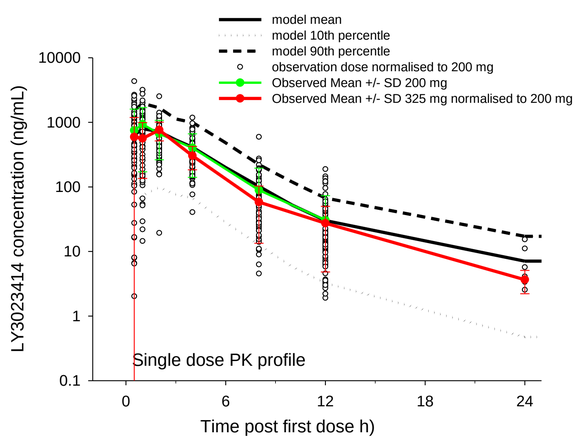
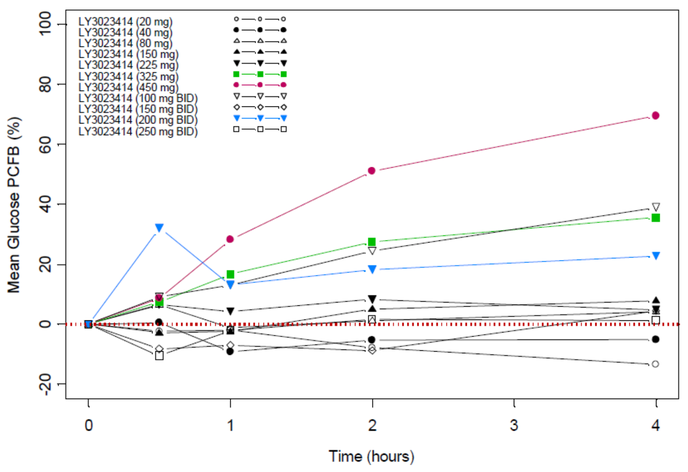


Figure 3: LY3023414 concentration versus time after 200 mg dose (observations normalized to 200 mg dose and model-simulated profiles)

Table 3: LY3023414 PK model parameters

	Mean (SEE%)	IIV (SEE%)
Ka (1/h)	0.54 (6.13)	
CL/F (L/h)	92 (7.53)	54.6 (30.0)
V1/F	140 (15.2)	144 (22.9)
Covariance (CL/F/V1/F)		70.4 (28.8)
Q/F	5.66 (15.2)	
V2/F	90.4 (28.0)	
BSA on CL	0.873 (51.0)[a]	
Limited auto-induction	0.989 (4.96)[b]	
Residual variability (%)		92 (10.6)

a: power model CL=92*((BSA/1.82)^0.873) ; median BSA 1.82
b: decrease clearance with time CL=92*((BSA/1.82)^0.873)*0.989 when time greater than 2 days
SEE standard error on the estimates (%), IIV inter-patient variability
CL/F clearance (following oral administration)
V1/F central volume of distribution
Q/F distribution clearance
V2/F peripheral Volume of distribution



Abbreviations: BID = twice daily; PCFB = percent change from baseline.
Line for LY3023414 (100 mg BID) is based on data from 1 patient only.

Figure 4: mean glucose percent change from baseline

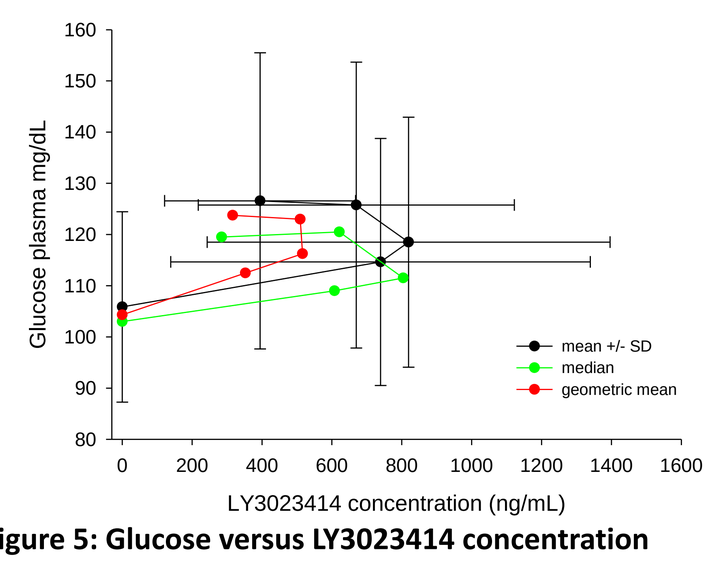


Figure 5: Glucose versus LY3023414 concentration

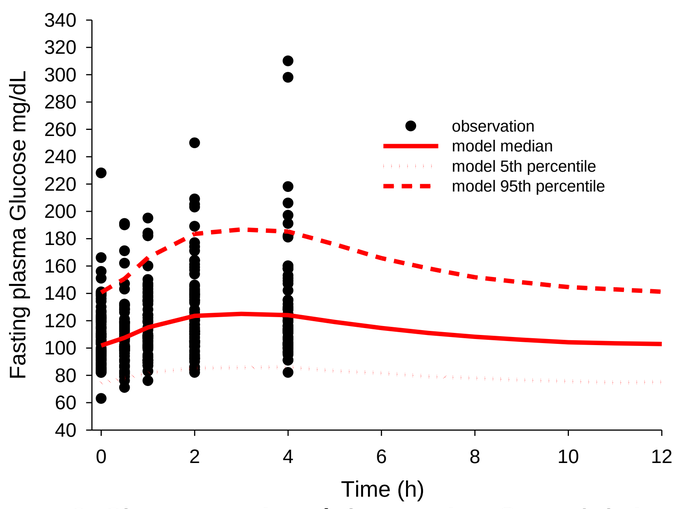


Figure 6: Glucose vs time (observation & model simulation)

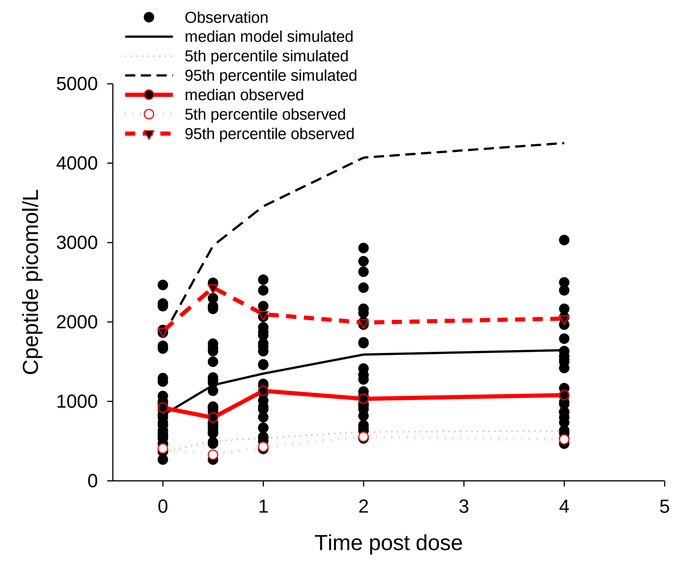


Figure 7: C-peptide vs time (observation & model simulation)

Table 4: Glucose C-peptide model parameters

	Mean (SEE%)	IIV (SEE%)
GL_baseline (mg/dL)	102 (1.86)	15.3 (21.4)
KEG (1/h)	0.788 (22.6)	
EMAL (no unit)	0.991 (19.8)	
LY50 (ng/mL)	852 (27.1)	71.2 (42.9)
GAMMA	1.5 (16.5)	
Residual variability glucose (%)		11.9 (12.2)
Cpep_baseline (pMol)	824 (8.51)	51.1 (16.5)
KEC (1/h)	16.1 (188)	
EMAG (no unit)	2.65 (14.5)	
GL50 (mg/dL)	129 (5.78)	
GAMMG	8.88 (12.5)	
Residual variability C-peptide (%)		41.0 (11.2)

SEE standard error on the estimates (%), IIV inter-patient variability
KEG – output rate of Glucose
EMAL – maximum increase in glucose input rate under LY
LY50 – LY concentration leading to 50 % of maximum increase in Glucose input rate
GAMMA – hill coefficient for the relationship between glucose input rate and LY
Initial condition KAG0=KEG*GL_baseline;
KAG= KAG0+(EMAL*CLY**GAMMA/(LY50**GAMMA+CLY**GAMMA))*KAG0, under LY
KEC - output rate of C-Peptide
EMAG - maximum increase in C-Peptide input rate under LY treatment
GL50 – Glucose concentration leading to 50 % of maximum increase in Cpep input rate
GAMMG – hill coefficient for the relationship between C-pep input rate and GL
Initial condition KAC0=KEC*Cpep_baseline
KAC= KAC0+(EMAG*CGL**GAMMG/(GL50**GAMMG+CGL**GAMMG))*KAC0

Conclusion:

- LY does lead to mild and transient increase in glucose. This finding is consistent with mechanism of action of LY, inhibition of PI3K/mTOR pathway,
- The model developed will help to bring these data in perspective of the literature historical information of the daily variation in glucose due to meal consumption.
- Plan to further develop this model, as new data are available, in perspective of the long term assessment of glucose homeostasis, HbA1c.

References
[1] https://www.cellsignal.com/contents/science-pathway-research-cellular-metabolism/insulin-receptor-signaling-pathway/pathways-irs
[2] Freckmann G, Hagenlocher S, Baumstark A, Jendrike N, Gillen R.C, Rössner K, Haug C. **Continuous Glucose Profiles in Healthy Subjects under Everyday Life Conditions and after Different Meals/** J Diabetes Sci Technol (2007) 1(5) 695-703