

Circadian timing regimen for alpelisib (BYL719), a selective inhibitor of the class Ia PI3K isoform alpha to maximize therapeutic index

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References

1. Juric et al, "Phase I study of the PI3K α Inhibitor BYL719, as a Single Agent in Patients with Advanced Solid Tumors (AST)", *Annals of Oncology* (2014), 25 (Supp. 4)
2. Brockway et al, "Fully Implantable Arterial Blood Glucose Device for Metabolic Research Applications in Rats for Two Months", *J Diabetes Sci Technol* (2015), 9(4):771-81

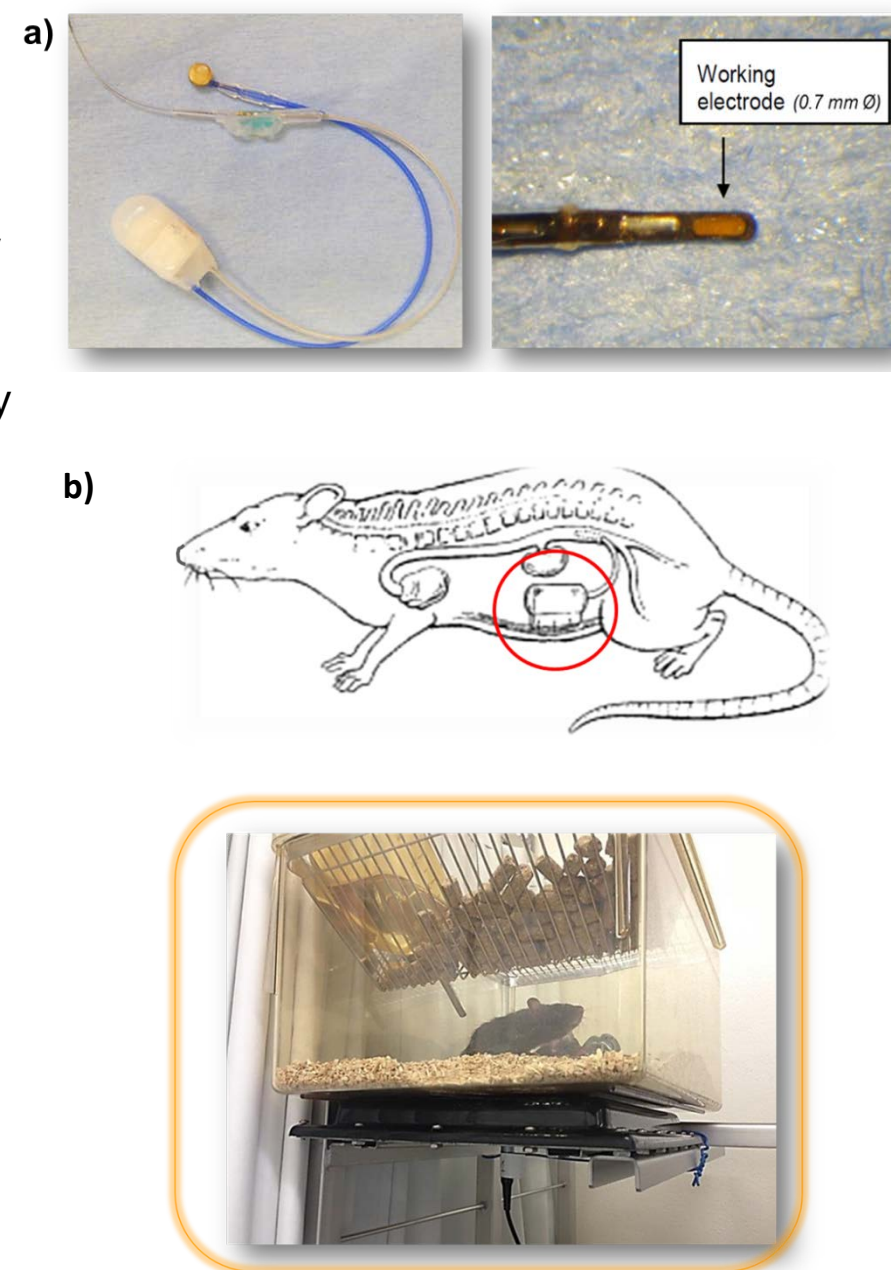


Introduction

- More than 85% of oncology preclinical agents entering clinical trials fail to demonstrate sufficient safety or efficacy to gain regulatory approval.
- This high failure rate highlights a poor prediction of safety vs antitumor efficacy (Therapeutic Index) in pre-clinical models.
- BYL719 given in the morning is facing on-target tolerability issues (hyperglycemia) in clinical trials limiting the dose being administered to patient (1).
- As glucose metabolism is highly impacted by circadian rhythms in patients and rodents, we have decided to adopt an integrative circadian-timing approach in our pre-clinical models to interrogate the benefit of morning vs evening dosing for BYL719.
- By using a newly developed radio-telemetry technology (2), we were able to record in real time and 'around-the-clock' blood glucose levels in stress-free, freely moving rats dosed with BYL719 at different regimens.

The new radio-telemetry approach using the HD-XG transmitter from DSI in paired-housed rats:

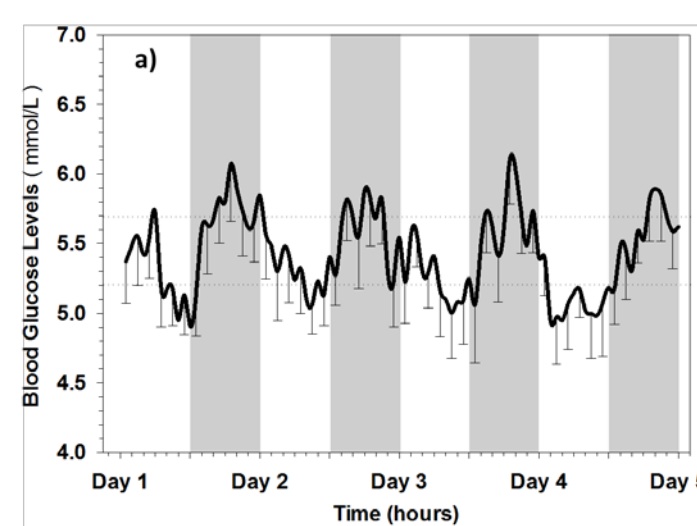
The 1.4cc telemetry device (a) provides direct continuous blood glucose readings along with temperature and activity for 4 weeks or longer. The device was evaluated in Brown Norway rats. Each animal was surgically instrumented with glucose sensors in the abdominal aorta and the device placed in the intraperitoneal cavity (c). Continuous glucose readings were recorded with the Dataquest A.R.T. data acquisition system in paired housed BN rats (d). Reference glucose values were measured from tail vein blood samples using the Nova Biomedical StatStrip® Glucose Meter.



Assessment of baseline blood glucose levels in BN rats:

Diurnal rhythms of glucose are highly reproducible over time

Glucose diurnal rhythms measured via radio-telemetry (a) over a period of 4 consecutive days are characterized by low inter-animal variability as well as by low intra-animal variability (values presented are mean \pm SEM, n=9).

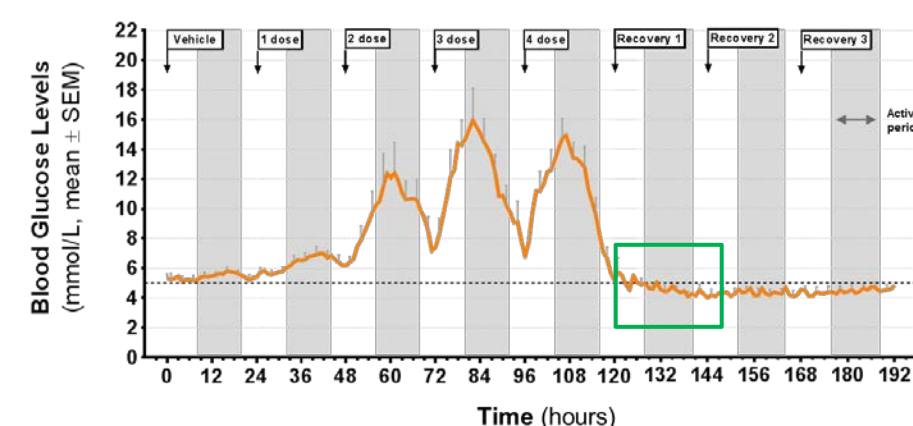


BYL719 (POC declared in 2012) is facing on-target tolerability issues (hyperglycemia) in clinical trials limiting the dose of BYL719 being administered to patient. As glucose metabolism (metabolic homeostasis) is highly impacted by circadian rhythms in patients and rodents, we have decided to adopt an integrative circadian-timing approach in our pre-clinical models to interrogate the benefit of morning vs evening dosing for BYL719.

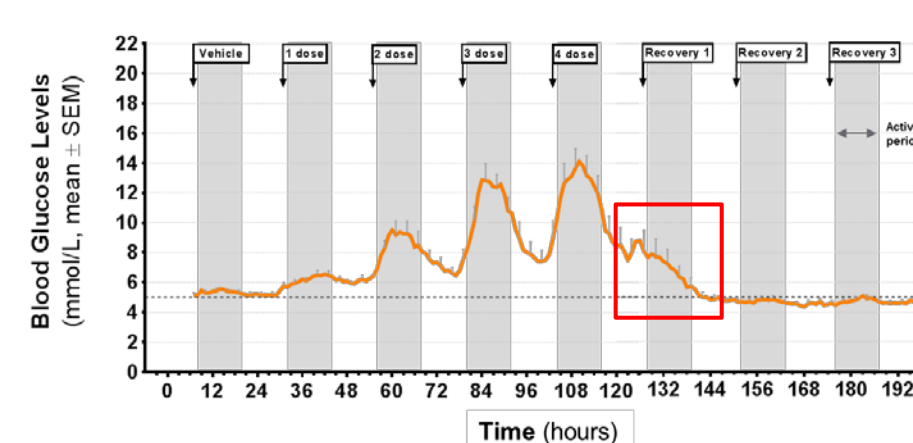
BYL719 effect on blood glucose levels in BN rats: Telemetry monitoring enable to measure increase in blood glucose levels (hyperglycemia) in real-time

The dynamic profile of hyperglycemia observed after active or inactive period dosing of BYL719 (50 mg/kg qd p.o.) at day 1 or 4 (at steady state) were similar. Dosing before the inactive phase (10 a.m.) allowed blood glucose to normalize in between 2 doses, which could not be achieved when dosing before the active phase (5 p.m.). After treatment discontinuation a significant hyperglycemia remained for a period up to 12h in the group dosed before the active phase (5 p.m.).

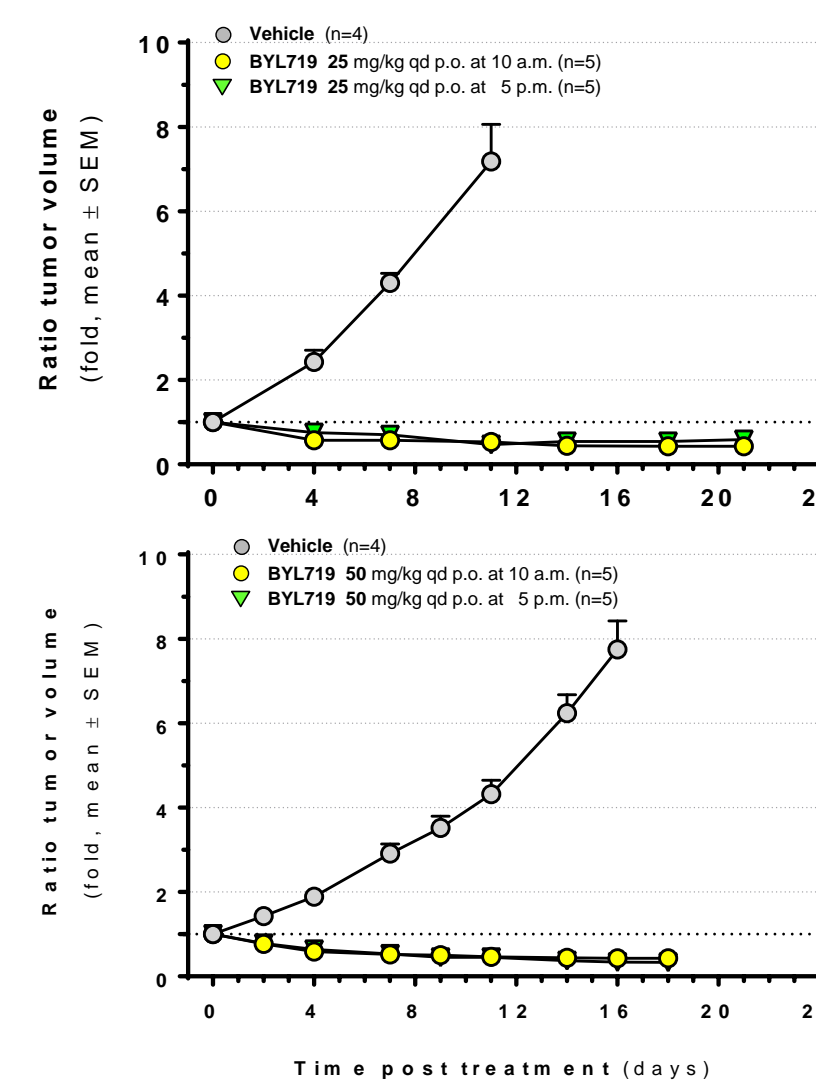
- Dosed at 10 a.m. before the inactive period (n=11)



- Dosed at 5 p.m. before the active period (n=9)

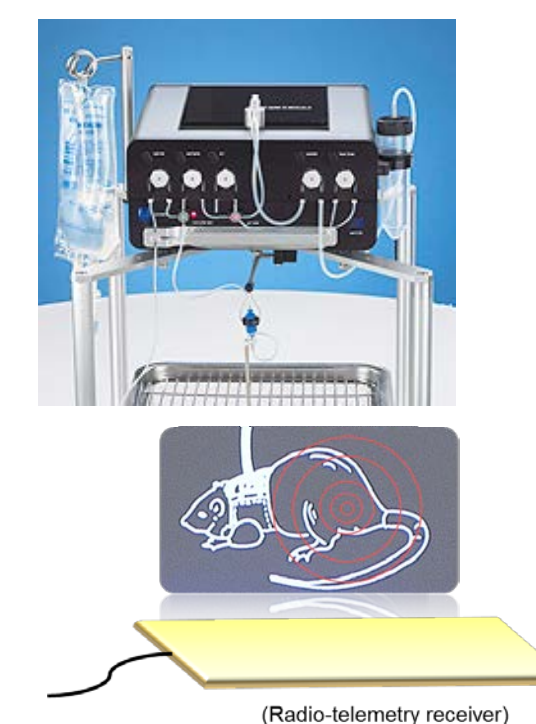


Comparison of evening vs morning dosing of BYL719 on efficacy in BN rats:

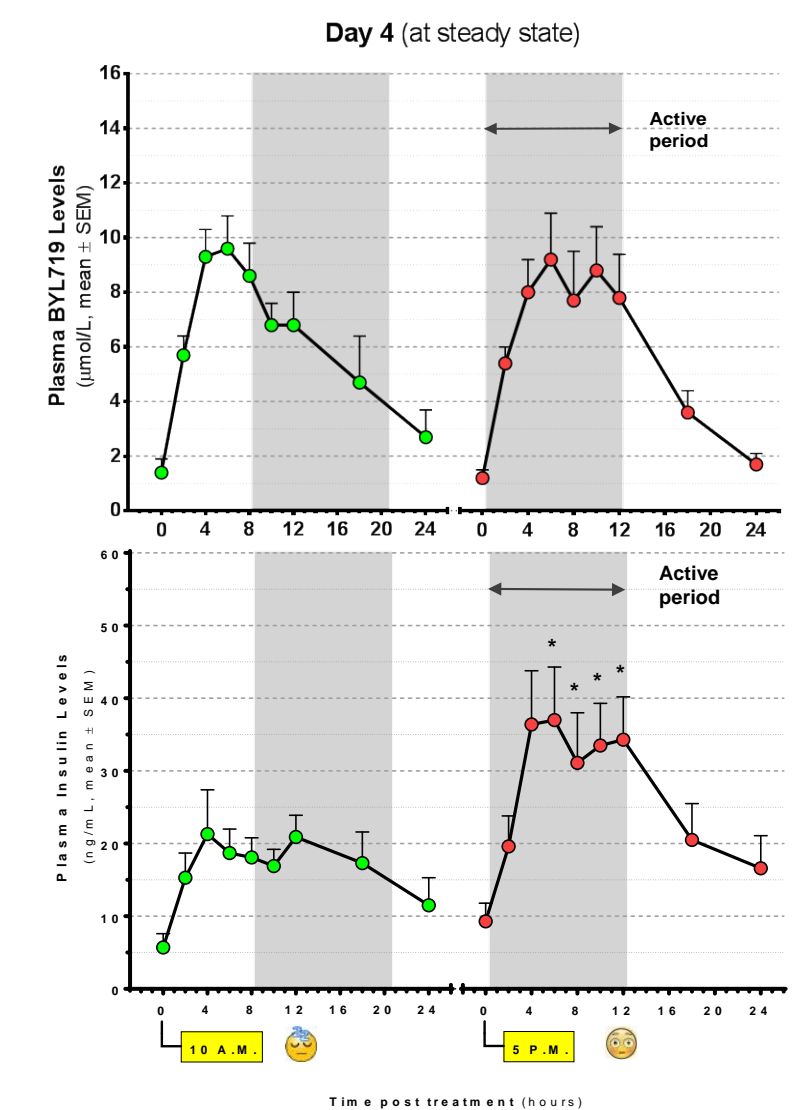


Evening dosing is as efficacious as morning dosing at clinically relevant doses in Rat1myr110 α tumor bearing nude rats.

Determination of pharmacokinetic (PK) parameters of BYL719 in freely moving catheterized BN rats using automated blood sampling (ABS) technology:



Plasma PK profile assessed in conscious freely moving BN rats connected to an ABS system at day 4 (steady state) of treatment with BYL719 (50 mg/kg qd p.o.) at 10 AM



(inactive phase) or 5 PM (active phase) did not revealed any significant differences (n= 4 to 9 per time point). However, plasma insulin levels were significantly enhanced.

Conclusions

- The HD-XG glucose telemetry implant offers a novel solution to obtain continuous, real-time, blood glucose measurements in laboratory animals in preclinical research up to 84 days.
- Circadian "evening" BYL719 dosing is associated with a better control of glycaemia and with a better outcome in vivo (enhanced tolerability without impacting efficacy). Clinically this could translate to better compliance and longer time on treatment hence better efficacy for patient.
- Based on these findings we could recommend optimized treatment schedules for future combination experiments in the clinic with BYL719.