

# Characterization of metabolic response to AG-348, an allosteric activator of red cell pyruvate kinase, in healthy volunteers and pyruvate kinase deficiency patients

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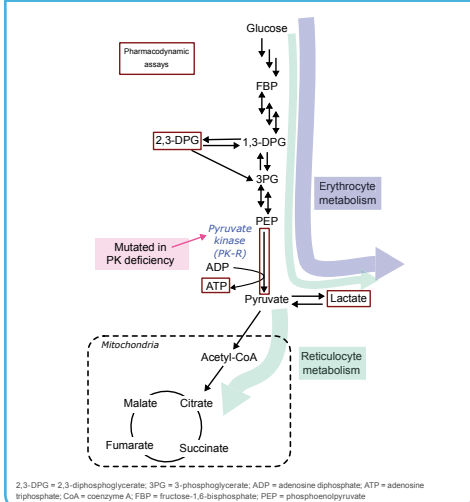
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## BACKGROUND

**PK deficiency**

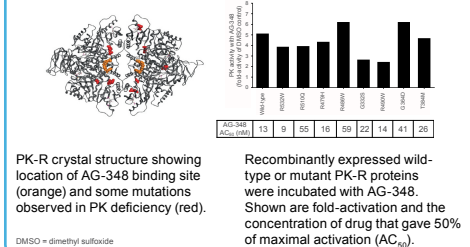
- Pyruvate kinase (PK) deficiency is a glycolytic enzymopathy that causes lifelong chronic hemolytic anemia.
- PK deficiency is caused by abnormalities of the PK red blood cell isoform R (PK-R) due to mutations in the *PKLR* gene.
- Mutations in PK-R typically affect protein stability, catalytic activity, or both, which adversely affects glycolysis and leads to severe energy starvation in red blood cells.

## Figure 1. Glycolytic pathway



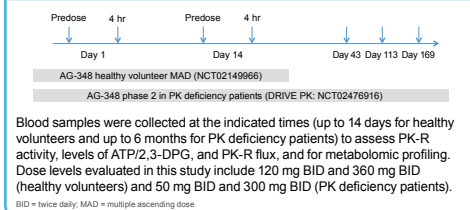
## Figure 2. AG-348 is a first-in-class allosteric activator of PK-R and is in clinical development to treat PK deficiency

Phase 1 studies of AG-348 in healthy volunteers (NCT02108106, NCT02149966) have been completed, and a phase 2 study in patients with PK deficiency is ongoing (DRIVE PK: NCT02476916).

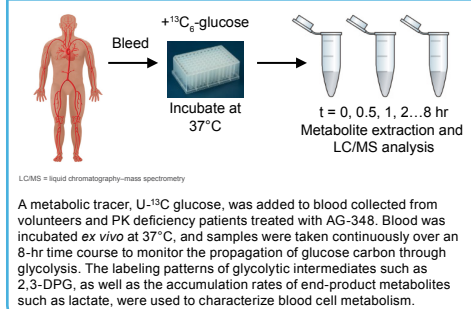


## METHODS

## Figure 3. Metabolic profiling and stable isotope tracing experiments were conducted in blood from healthy volunteers (n=16) and PK deficiency patients (n=8) receiving AG-348

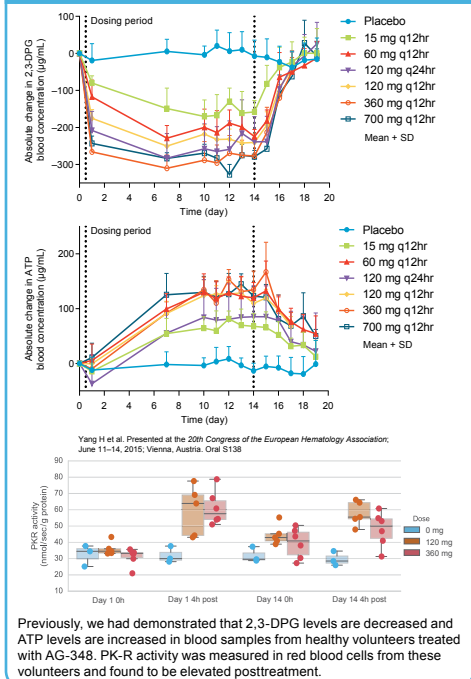


## Figure 4. Ex vivo flux assay

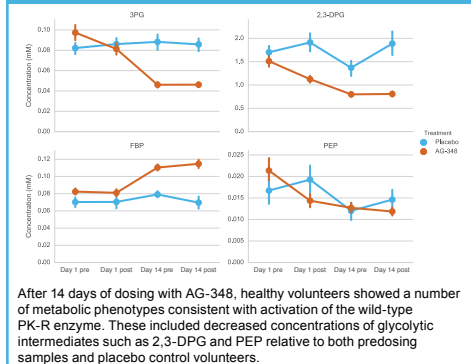


## RESULTS

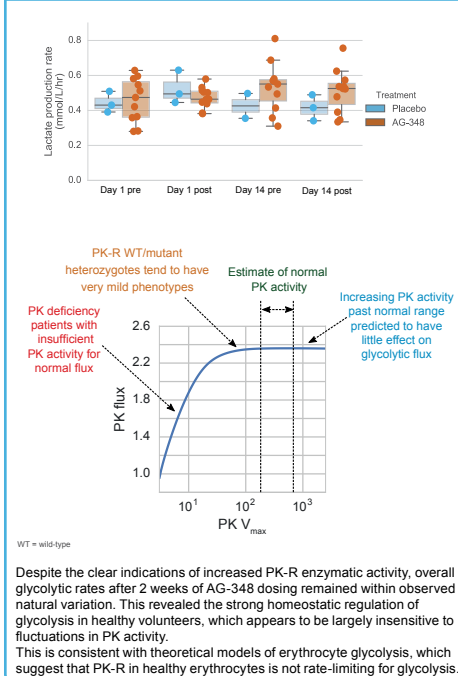
## Figure 5. AG-348 increases PK-R activity in healthy volunteers



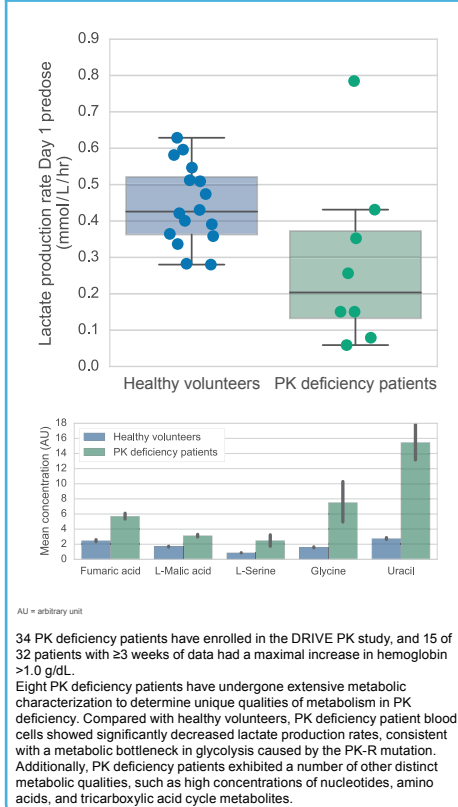
## Figure 6. Healthy volunteers show metabolic markers of increased PK-R activity



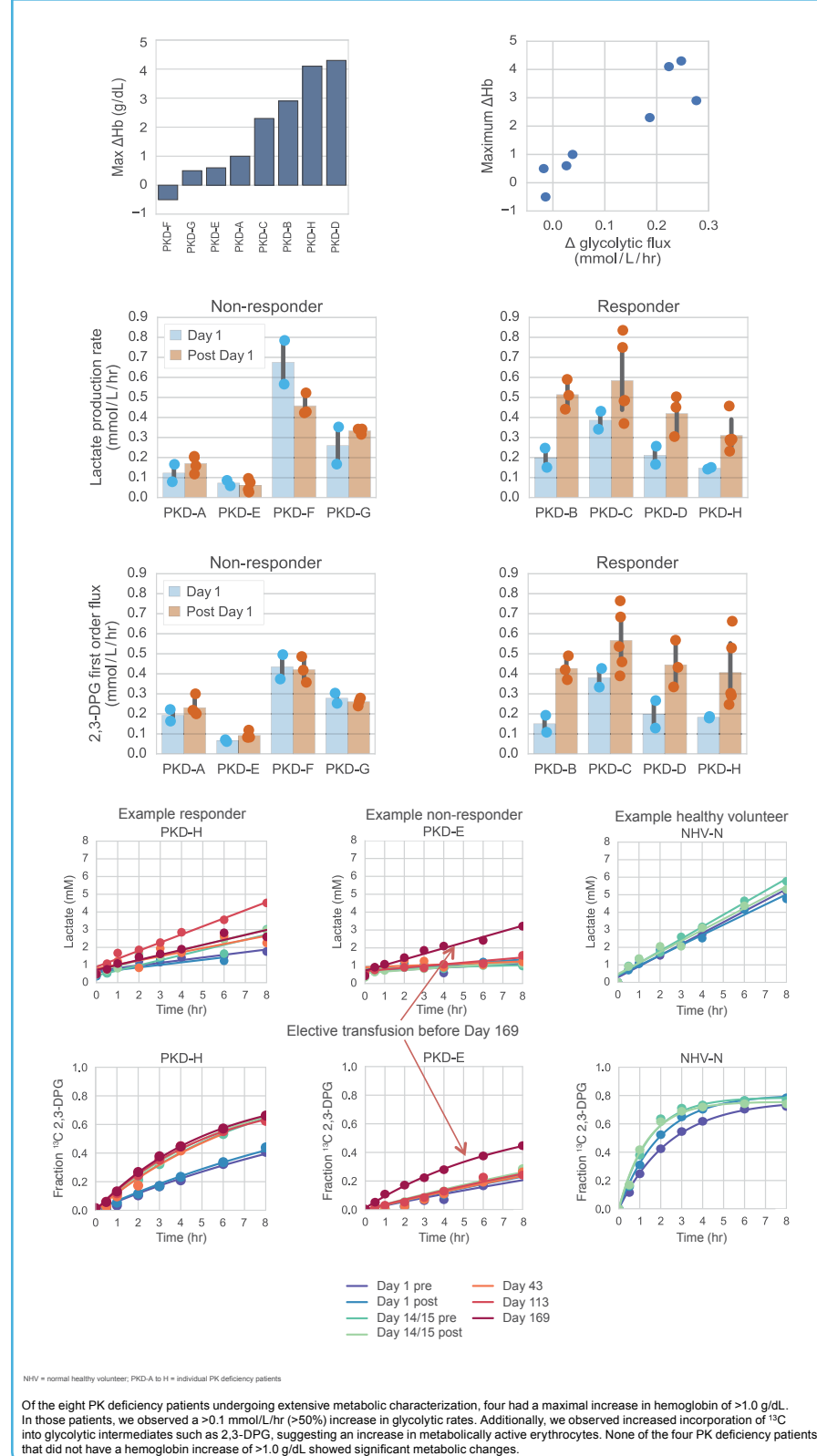
## Figure 7. Overall glycolytic rates in healthy volunteers after PK-R activation remained normal



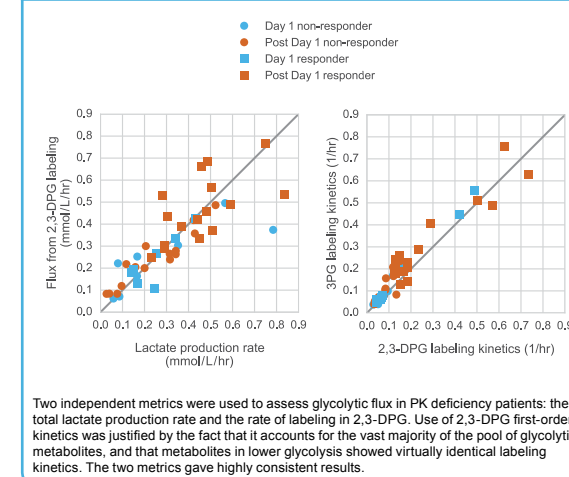
## Figure 8. Metabolic analysis reveals reduced glycolytic flux in PK-deficient blood



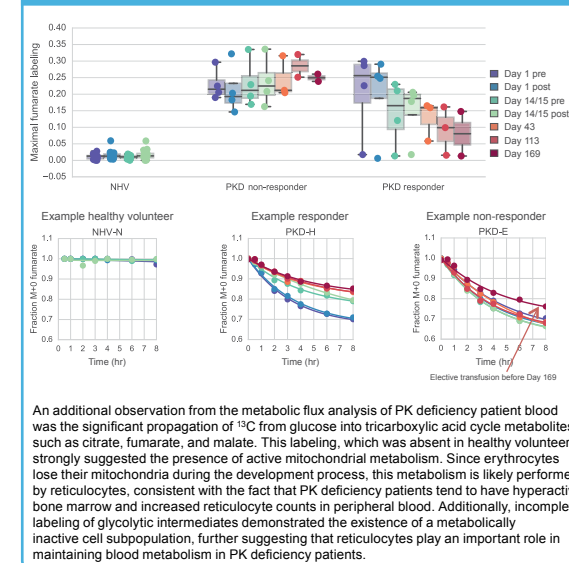
## Figure 9. AG-348 rescues metabolic phenotypes in responsive patients



## Figure 10. Independent metrics of glycolytic flux in PK deficiency patients show consistent results



## Figure 11. Metabolic markers of immature red cells are reduced in PK deficiency patients that respond to AG-348



## CONCLUSIONS

- A >50% increase in glycolytic flux was observed in PK deficiency patients treated with AG-348 who had a hemoglobin increase >1.0 g/dL, but was not observed in patients without such an increase.
- Metabolic markers of immature red cells are reduced in PK deficiency patients that respond to AG-348.
- Strong homeostatic regulation of overall rates of glycolysis was observed in healthy volunteers, even in the presence of activated PK-R.
- These data demonstrate that hemoglobin increases in PK deficiency patients treated with AG-348 are associated with increased red cell glycolysis.

**Disclosures**  
This study was funded by Agios Pharmaceuticals, VC, KJ, PA, AJ, HK, TPR, AJB, LD, LS, CK, Agios - employment and stockholder; MC, EM, Agios - employment and stockholder at time of study; Editorial assistance was provided by Helen Varley, PhD, CMPP, Excel Scientific Solutions, Horsham, UK, and supported by Agios.