Effects of AG-348, a Pyruvate Kinase Activator, on Anemia and Hemolysis in Patients with Pyruvate Kinase (PK) Deficiency: Data from the DRIVE PK Study

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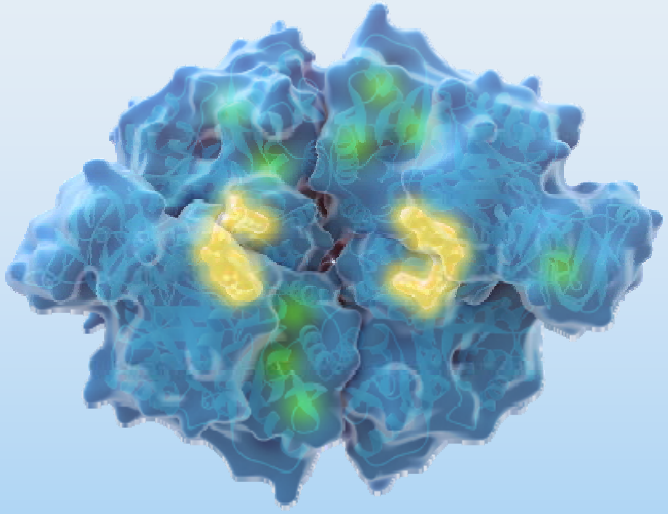
PK deficiency and the role of AG-348: an allosteric activator of pyruvate kinase R

Description	• Presents at any time of life, as early as the neonatal period with severe hemolytic anemia • Estimated prevalence ranges from ~1:20K to ~1:485K[1–4]
Etiology	• Caused by mutations in the *PKLR* gene coding for erythrocyte pyruvate kinase (PK-R)
Disease Burden	• Lifelong hemolytic anemia • Iron overload and jaundice • Infection risk post-splenectomy
Diagnosis/ Treatment	• PK-R enzyme activity and/or genetic testing • Supportive treatment: transfusions, splenectomy, iron chelation

Active PK-R is a tetramer; mutations (green) decrease the catalytic activity



AG-348 (yellow) binds at the PK-R dimer-dimer interface, away from the active site and the most common mutations

Please see Posters 1263, 1264 and 2452 at the current meeting for more information on PK-R activators

Grace R et al. *Am J Hematol* 2015;90(9):825-30; [1]Mohrenweiser HW *PNAS* 1981;78(8):5046-50; [2]Carey PJ et al. *Blood* 2000;96(12):4005-6; [3]Beutler E & Gelbart T *Blood* 2000;95(11):3585-8; [4]deMedicis et al. *Hum Hered* 1992;42(3):179-83

Study design

Open-label, global phase 2 study: 14 centers in the US, Canada, and EU

Transfusion-independent adults with PK deficiency
(ClinicalTrials.gov NCT02476916) n=25 in each arm

Randomization
Stratified by PK-R genotype
(none excluded)

- **Arm 1**
  300 mg BID
- **Arm 2**
  50 mg BID

6 month core dosing period

1 2 3 6 9 12 16 20 24
Assessment points (weeks)

Primary endpoints:

- Safety and tolerability

Secondary endpoints:

- Pharmacokinetics of AG-348
- PD response: ATP, 2,3-DPG
- **Indicators of clinical activity**: hemoglobin, reticulocyte count, and other hematologic parameters

Transfusion independence = no more than 3 units transfused in 12 months prior to the first day of study dosing and no transfusions within 4 months of first day of study dosing

Extension arm

All patients provided written informed consent. BID = twice daily; PD = pharmacodynamic

Demographics and disposition

- Study initiated June 2015; data cut-off September 23, 2016
- Evaluable analysis set: ≥3 weeks of data (n=32)
- Safety analysis set: received at least 1 dose of AG-348 (n=34)
- 13 patients ongoing in the core period (as of September 23, 2016)
  - Early discontinuations in the core period due to: relocation (n=1), AEs (n=3)
- Of the 17 patients who completed the core period, 15 enrolled in the extension period
- 1 patient discontinued in extension period due to physician decision (lack of efficacy)

Characteristics	50 mg BID, n=17	300 mg BID, n=17	Total, N=34
Men/women, n	11/6	9/8	20/14
Age in years, mean (range)	28.5 (19-45)	37.0 (20-61)	32.8 (19-61)
Race[a] white, n	15	15	30
Hemoglobin (Hb) baseline, g/dL, mean (SD, range)	9.8 (1.41, 7.6–12.4)	8.7 (1.37, 6.5–11.8)	9.2 (1.47, 6.5–12.4)
Duration of treatment, weeks, median (range)	24.7 (4.7–50.4)	24.0 (2.4–44.4)	24.4 (2.4–50.4)
Splenectomized, n	14	14	28

[a]Not reported in 2 patients, 2 patients were Asian; AE = adverse event; SD = standard deviation

Safety summary

- AG-348 was generally well tolerated; the majority of AEs were grade 1–2
  - No grade 4 AEs or deaths
  - 2 patients experienced serious AEs: Grade 2 osteoporosis; hemolysis and anemia due to discontinuation of the drug after a rapid Hb response (patient continued in the study)
  - 3 patients discontinued treatment due to AEs
  - DXA scan data (n=17) show high variability and are inconclusive

AEs, regardless of causality (occurring in >5 patients or assessed as Grade ≥3)	50 mg BID n=17		300 mg BID n=17		Total N=34	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients experiencing at least 1 AE, n	13	2	17	6	30	8
Headache	7	0	8	0	15	0
Nausea	7	0	7	0	14	0
Insomnia	3	1	10	1	13	2
Fatigue	3	0	3	0	6	0
Vomiting	2	0	4	0	6	0
Hypertriglyceridemia	0	0	4	3	4	3
Anaemia	1	1[a]	1	1[b]	2	2
Hypertension	0	0	1	1	1	1
Dizziness	2	0	1	1	3	1
Haemolysis	0	0	2	1[b]	2	1

[a]Grade 3 anemia, not a serious AE. [b]Grade 3 withdrawal hemolysis and anemia in 46-year-old woman due to abrupt drug withdrawal after a very fast Hb response

AEs were graded using National Cancer Institute Common Terminology Criteria, version 4.03. Hb = hemoglobin; DXA = Dual energy X-ray absorptiometry

Effect of AG-348 on hormones

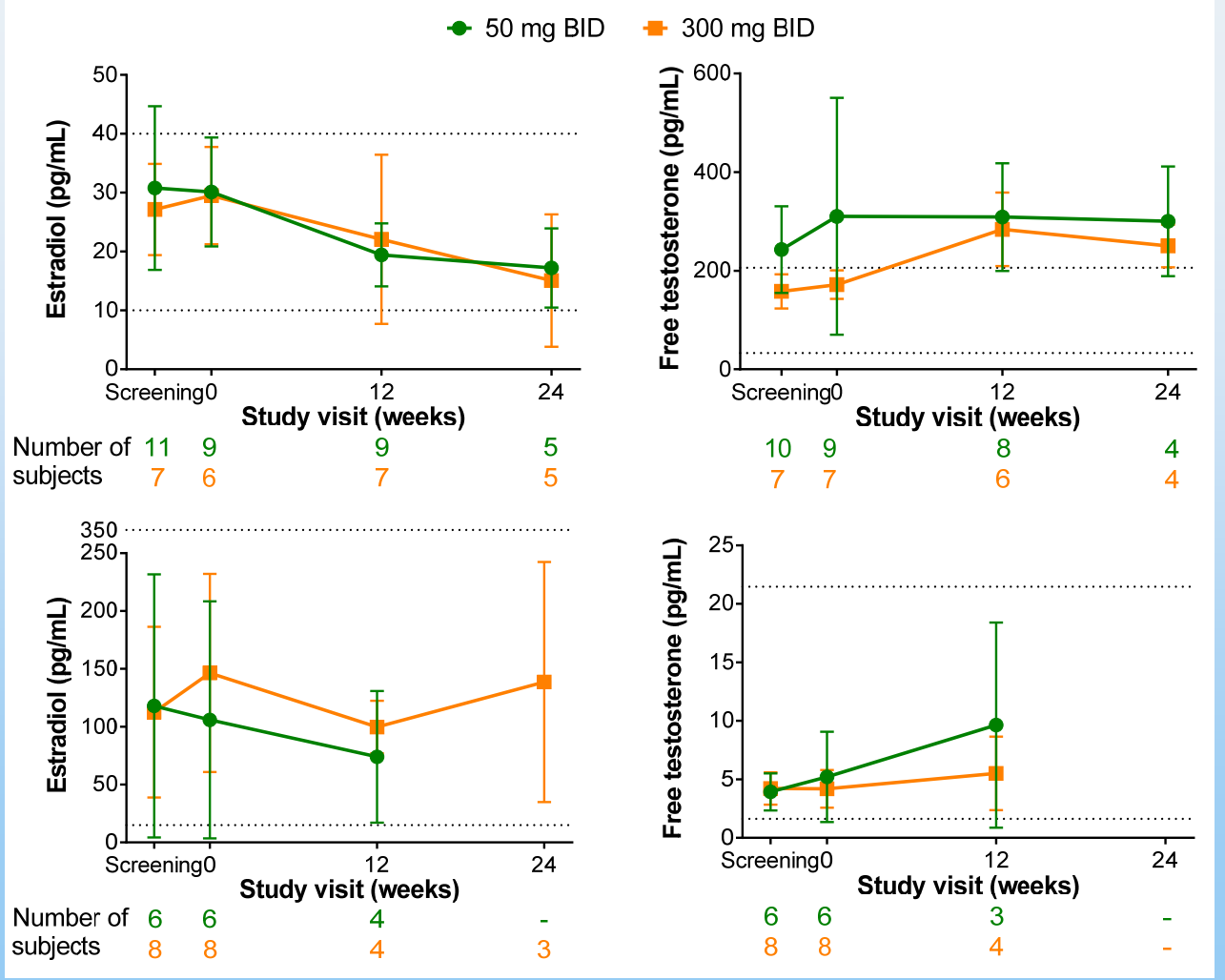
- Preliminary findings are consistent with aromatase inhibition by AG-348

Male

Hormone levels assessed at baseline, 12 and 24 weeks

Patients with available data shown

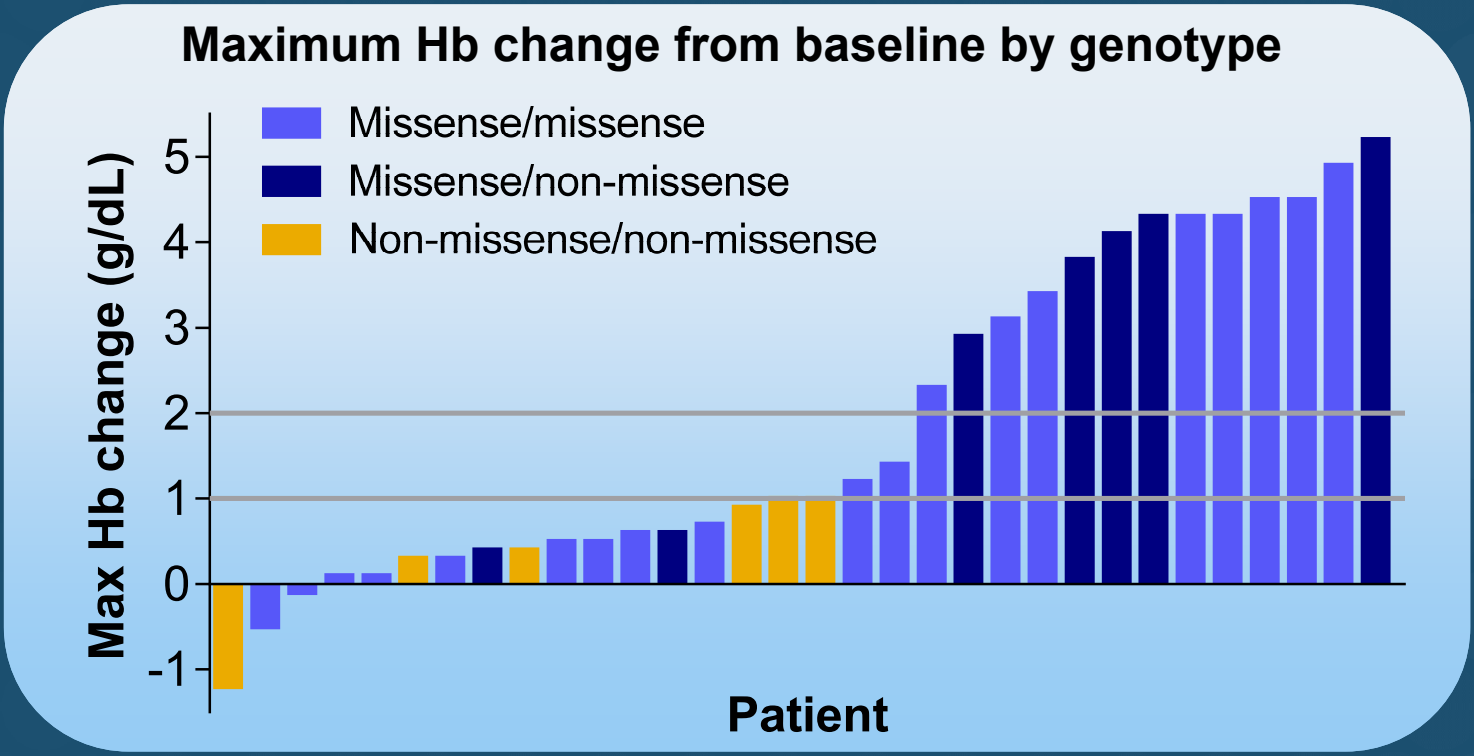
Female



Clinical Activity Results

Maximum increase in hemoglobin (Hb)

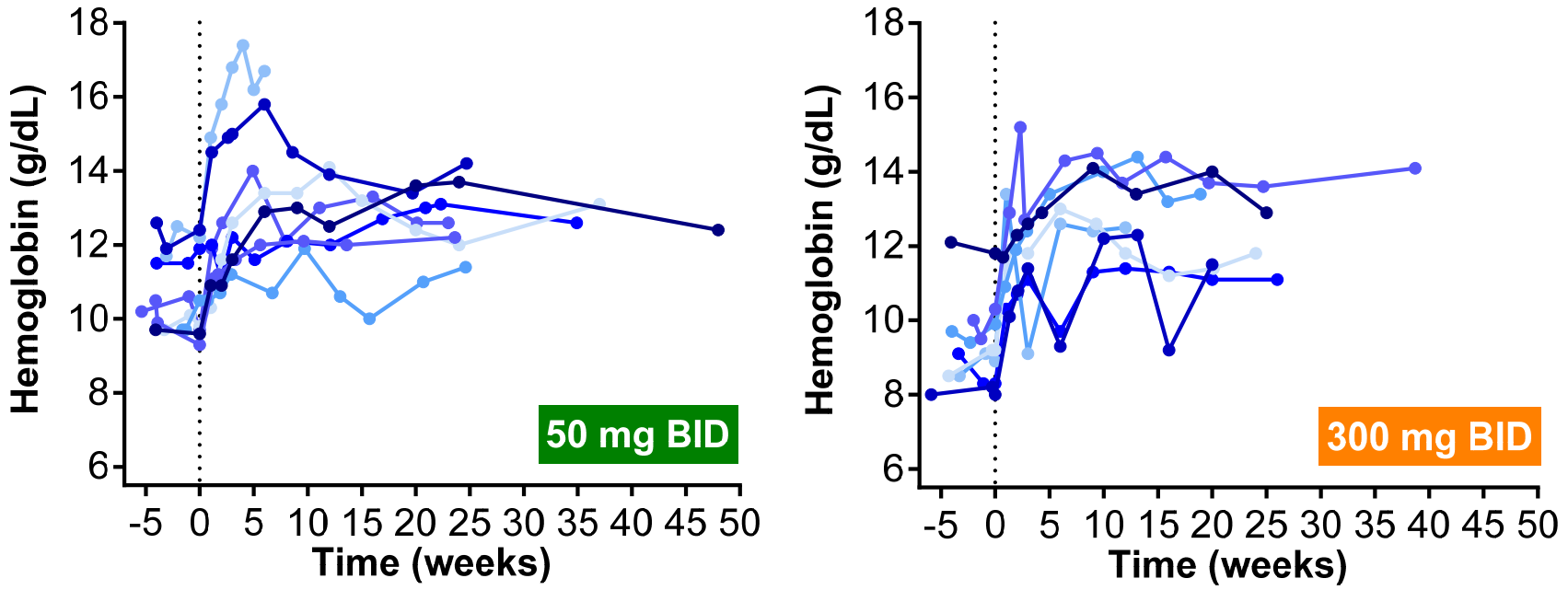
- 15 of 32 (47%) patients had a maximal increase in Hb >1.0 g/dL
  - 15 of 26 patients (58%) who had ≥1 missense mutation had a Hb response
- 5 patients homozygous for R479H (mis/mis; Amish) were non-responders
- Hb response and response maintenance are seen across a range of 4 doses
  - Robust Hb responses led to dose decreases with maintained Hb



Evaluable analysis set, ≥3 weeks of data

Hb increases are rapid and sustained

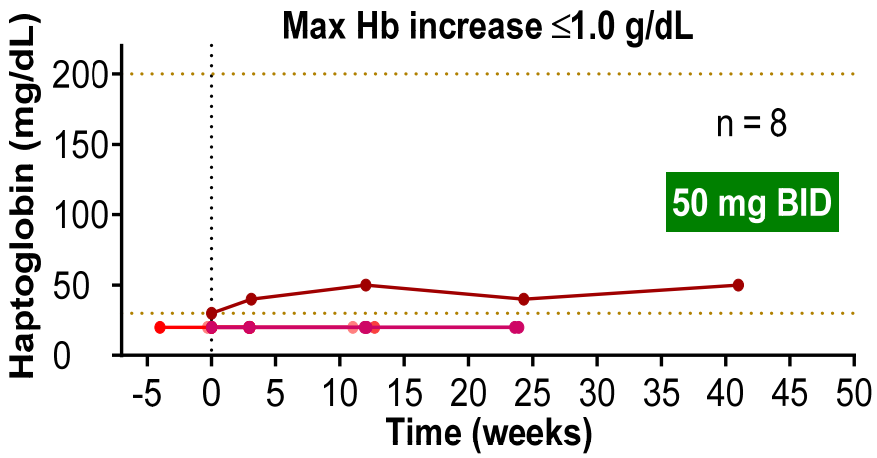
- In patients who had Hb increases >1.0 g/dL (n=15):
  - Median time to Hb increase >1.0 g/dL was 1.4 weeks (range, 1.1–21.0)
  - The mean maximum increase was 3.6 g/dL (range, 1.2–5.2)
- 10 patients had dose reductions: 5 due to rapid Hb increase[a]

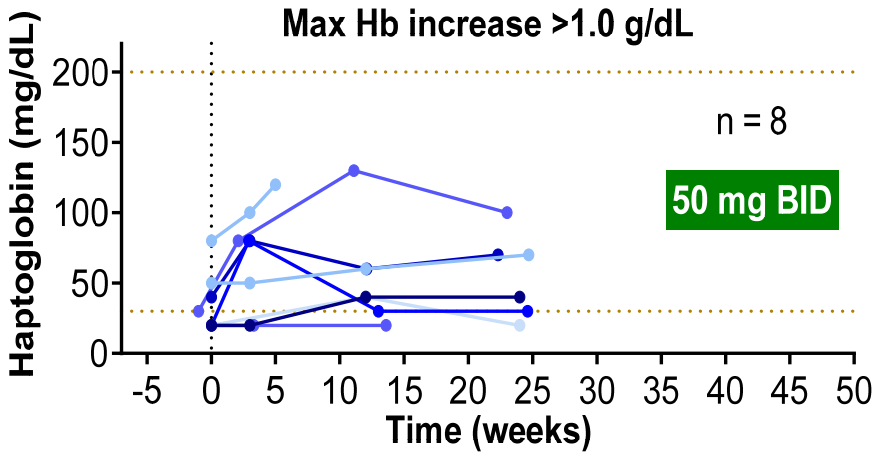


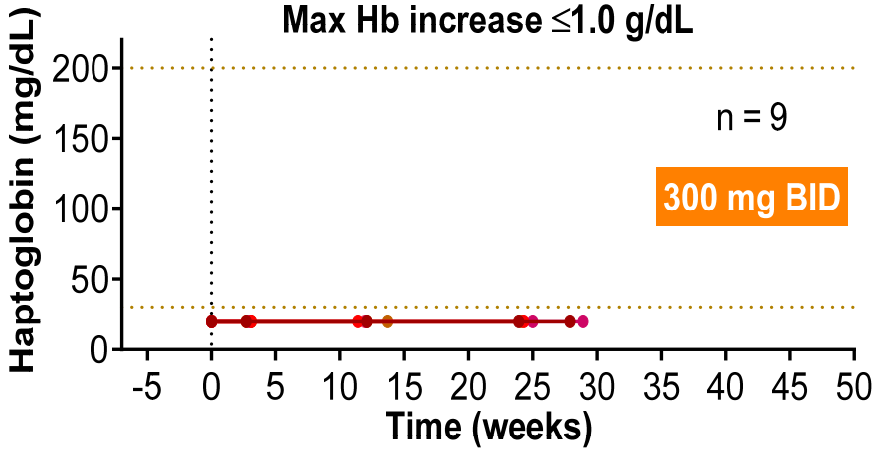
Responders n=15, each line represents an individual patient

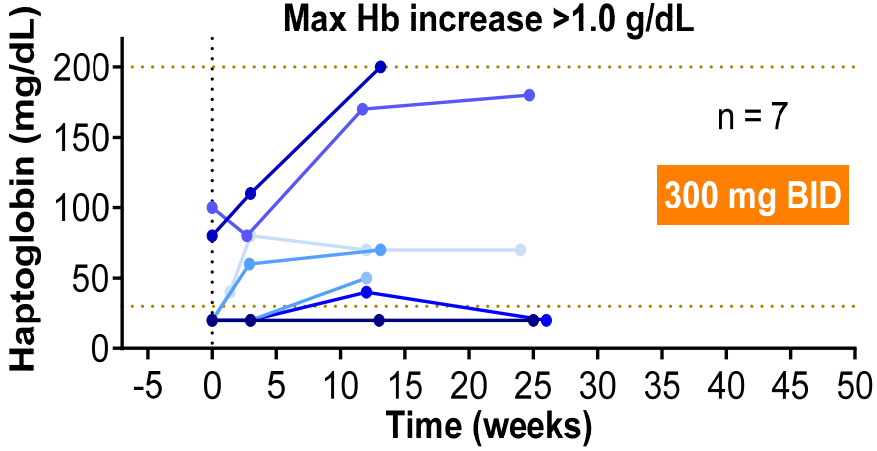
[a]Other dose reductions due to: AEs (n=3), self-reduction due to fatigue (n=1), taper prior to discontinuation (n=1)

Haptoglobin levels increase in responders, indicating decreased hemolysis









Normal reference low and high limits shown as horizontal dotted lines

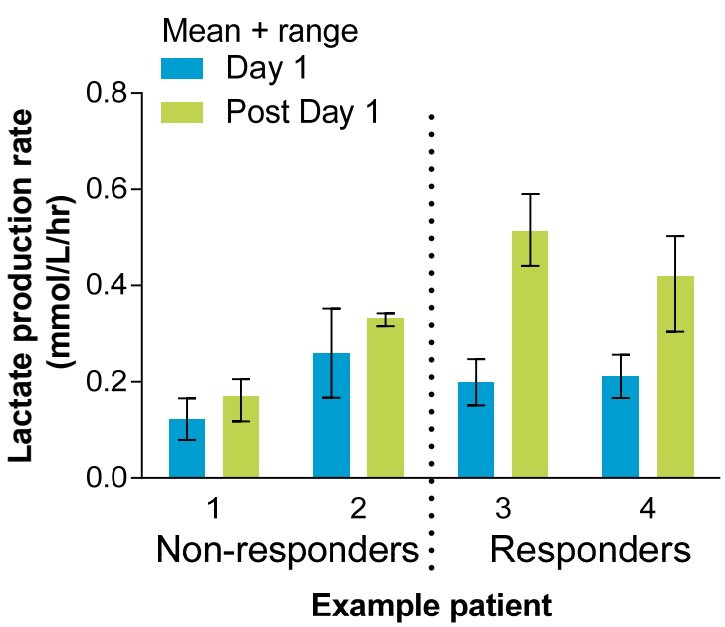
Pharmacodynamic Results

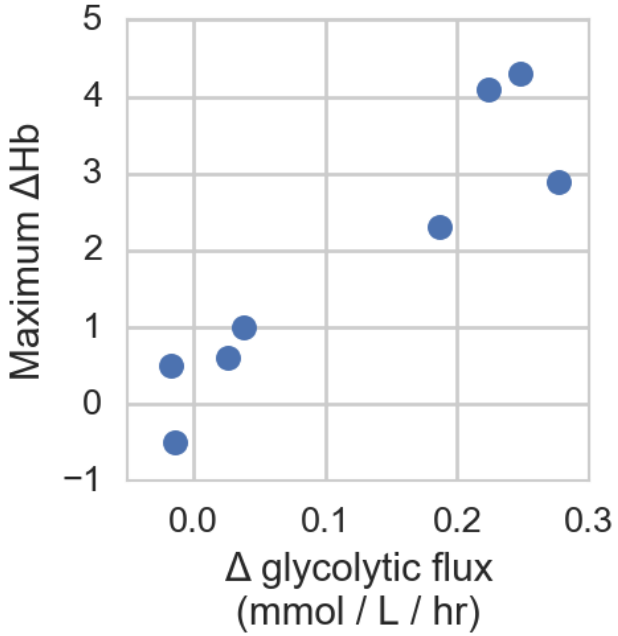
Patients with Hb increases also had increased rate of metabolism in PK-R pathway in peripheral blood

- Rate of metabolism of PK-R pathway was assessed in blood samples from a subset of patients pre and post treatment
- These data suggest a positive correlation between Hb change and change in glycolytic flux

Detailed metabolic characterization in blood from 8 patients

Glycolytic flux assessed *ex vivo* via incorporation of labelled glucose into the end product, lactate





Representative 4 patients shown here

N=8

DRIVE-PK conclusions

- AG-348 is a novel, first-in-class, PK-R activator in clinical testing as a potential disease-altering therapy to improve anemia in patients with PK deficiency
- Daily dosing with AG-348 for up to 6 months is well tolerated
  - Clinical significance of AG-348 aromatase inhibition is unclear
- AG-348 demonstrates clinically relevant rapid and durable increases in Hb in 47% of patients enrolled in the study
  - Hb increase is linked to activation of glycolytic pathway
  - Preliminary genotype-Hb response correlations were observed
- These data highlight the potential of PK-R activators as the first disease-altering treatment for patients with PK deficiency

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