Effects of AG-348, a pyruvate kinase activator, on anemia and hemolysis in patients with pyruvate kinase deficiency: early data from the DRIVE-PK study

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Disclosures

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- Christian Rose: Agios – study investigator
- D Mark Layton: Agios – study investigator
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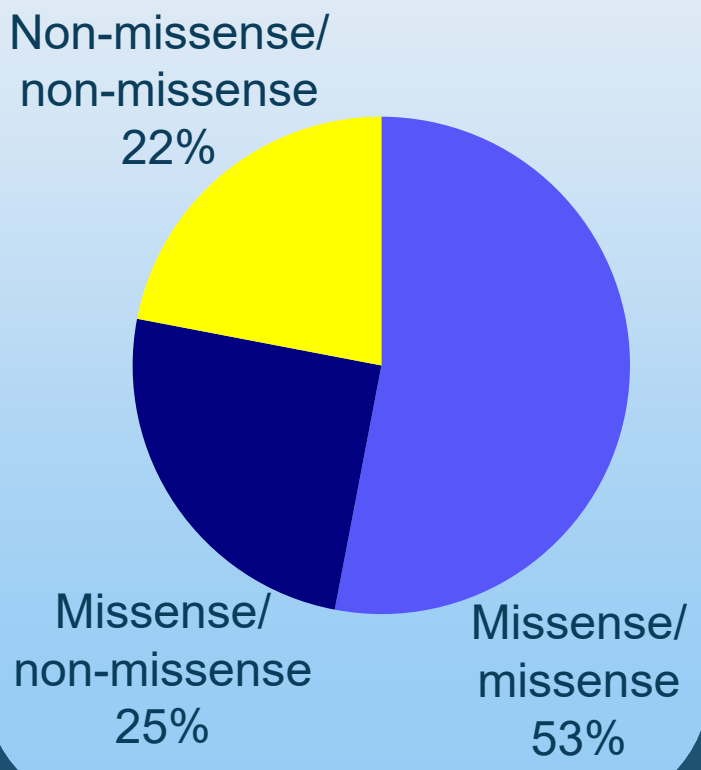
Pyruvate kinase (PK) deficiency: a severe congenital anemia

Description	• Presents in childhood with severe hemolytic anemia
Etiology	• Caused by mutations in the *PK-LR* 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

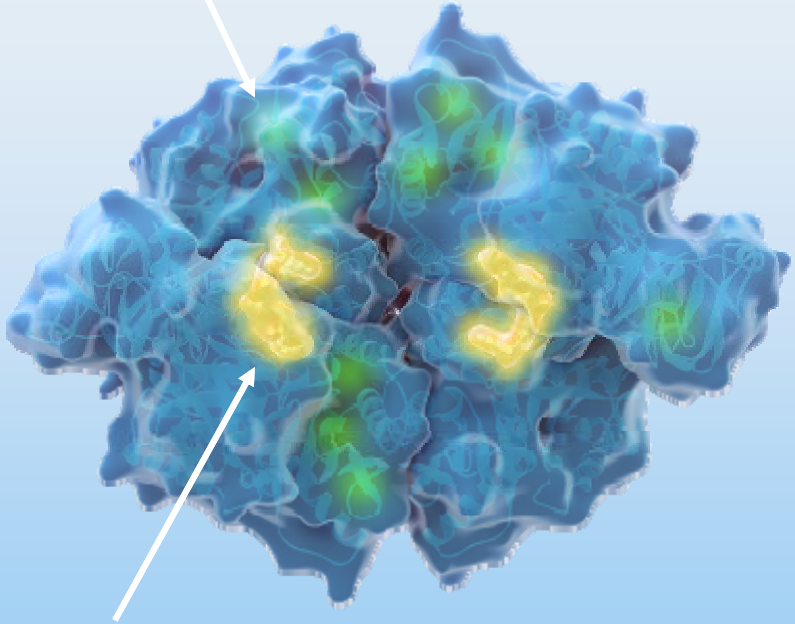
Type of *PK-LR* mutations found in 74 unrelated cases enrolled in the PK deficiency natural history study



Source: Grace R et al. *Am J Hematol* 2015;90(9):825-30; Bianchi P et al. 57th ASH Annual Meeting 2015, Abstract 3337

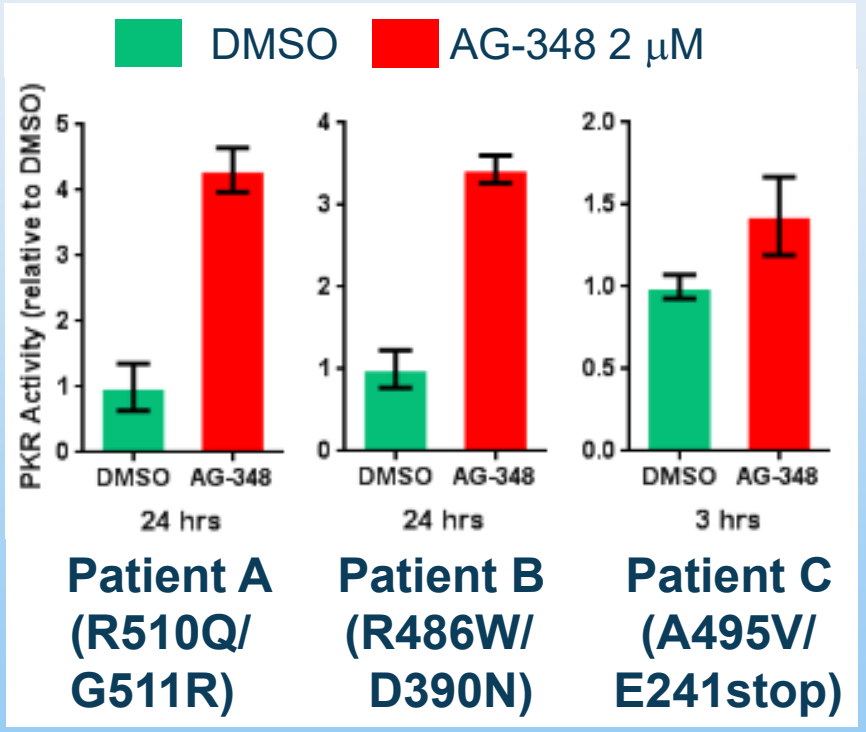
AG-348: allosteric activator of wild-type and mutant PK-R

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

AG-348 activates mutant PK-R in blood from PK deficient patients



Patient A (R510Q/ G511R)

Patient B (R486W/ D390N)

Patient C (A495V/ E241stop)

Study design

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

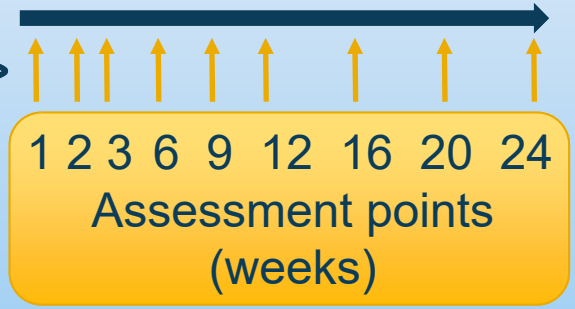
Transfusion-independent PK-deficient adults

(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



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 of red blood cells 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

- The study was initiated in June 2015; data cut-off 27 March 2016
- 18 patients have been treated, with no early discontinuations
- Three patients have completed the 24-week core period
  - Two remain on treatment in the extension arm

Characteristic	50 mg BID, n=9	300 mg BID, n=9	Total, N=18
Men/Women, n	7/2	5/4	12/6
Age in years, mean (range)	25.9 (19–41)	35.3 (22–61)	30.6 (19–61)
Race[a] white, n	8	9	17
Hemoglobin baseline, g/dL, mean (SD)	10.0 (1.5)	8.5 (1.6)	9.3 (1.7)
Duration of treatment, weeks, median (range)	10.7 (3.0–24.4)	10.9 (3.0–24.0)	10.8 (3.0–24.4)
Splenectomized, n	6	7	13

[a]Not reported in 1 subject

Safety and adverse event (AE) summary

- AG-348 was generally well tolerated; the majority of AEs were grade 1–2
  - One subject received a dose reduction due to rapidly increasing hemoglobin
  - One grade 2 'allergic reaction', successfully re-challenged with lower dose
  - One grade 2 AE of osteoporosis has been reported since the cut-off date
- No significant changes in ECGs and clinical safety laboratory parameters

	50 mg BID n=9	300 mg BID n=9	Total N=18
Subjects experiencing at least 1 AE, n	7	8	15
Most frequent AEs (≥3 subjects), n			
Nausea	4	5	9
Headache	2	2	4
Hot flush	1	2	3
Insomnia	0	3	3
Subjects experiencing at least 1 drug-related AE, n	6	7	13
Subjects experiencing at least 1 serious AE	0	0	0
Subjects experiencing at least 1 grade ≥3 AE[a]	0	2	2
Subjects experiencing at least 1 grade ≥3 drug-related AE	0	1	1

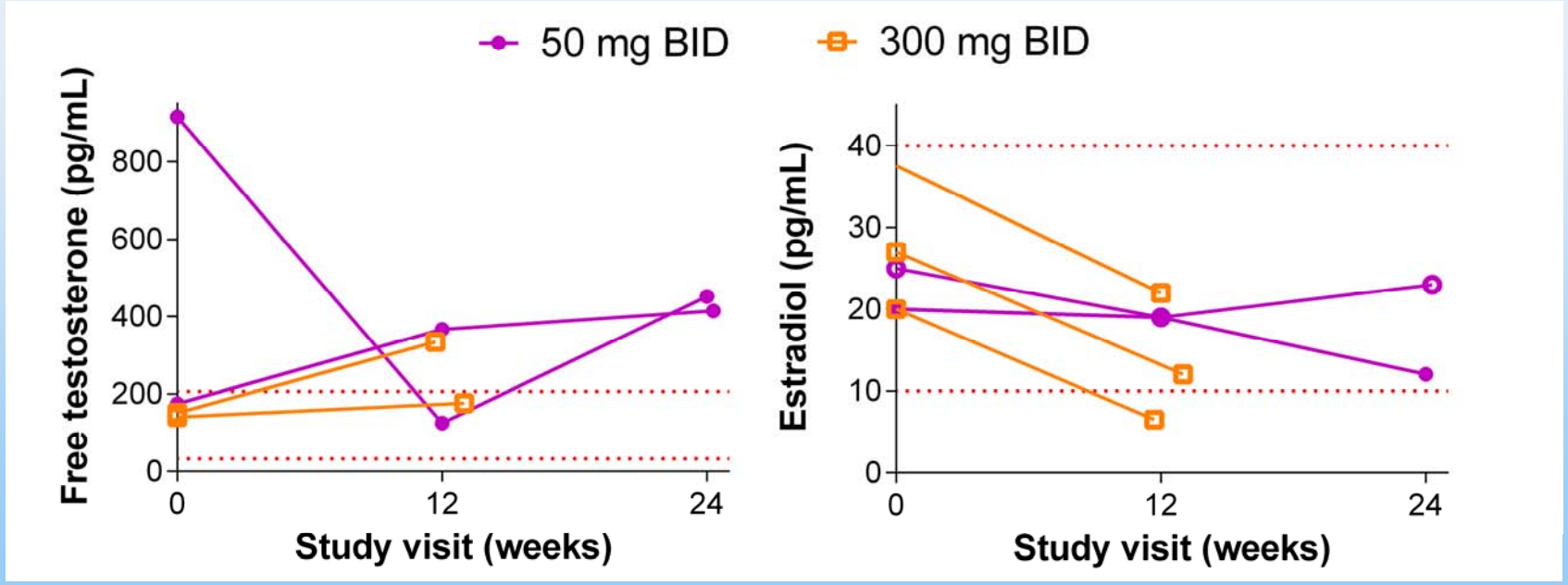
AEs were graded using National Cancer Institute Common Terminology Criteria, version 4.03

[a]Two grade 3 events (unrelated hypertension, related hypertriglyceridemia)

Effect of AG-348 on sex steroids

- Sex steroids were assessed at baseline, week 12 and week 24
- An upward trend in free testosterone and a downward trend in estradiol were observed in male patients

Hormone levels in male patients with available data

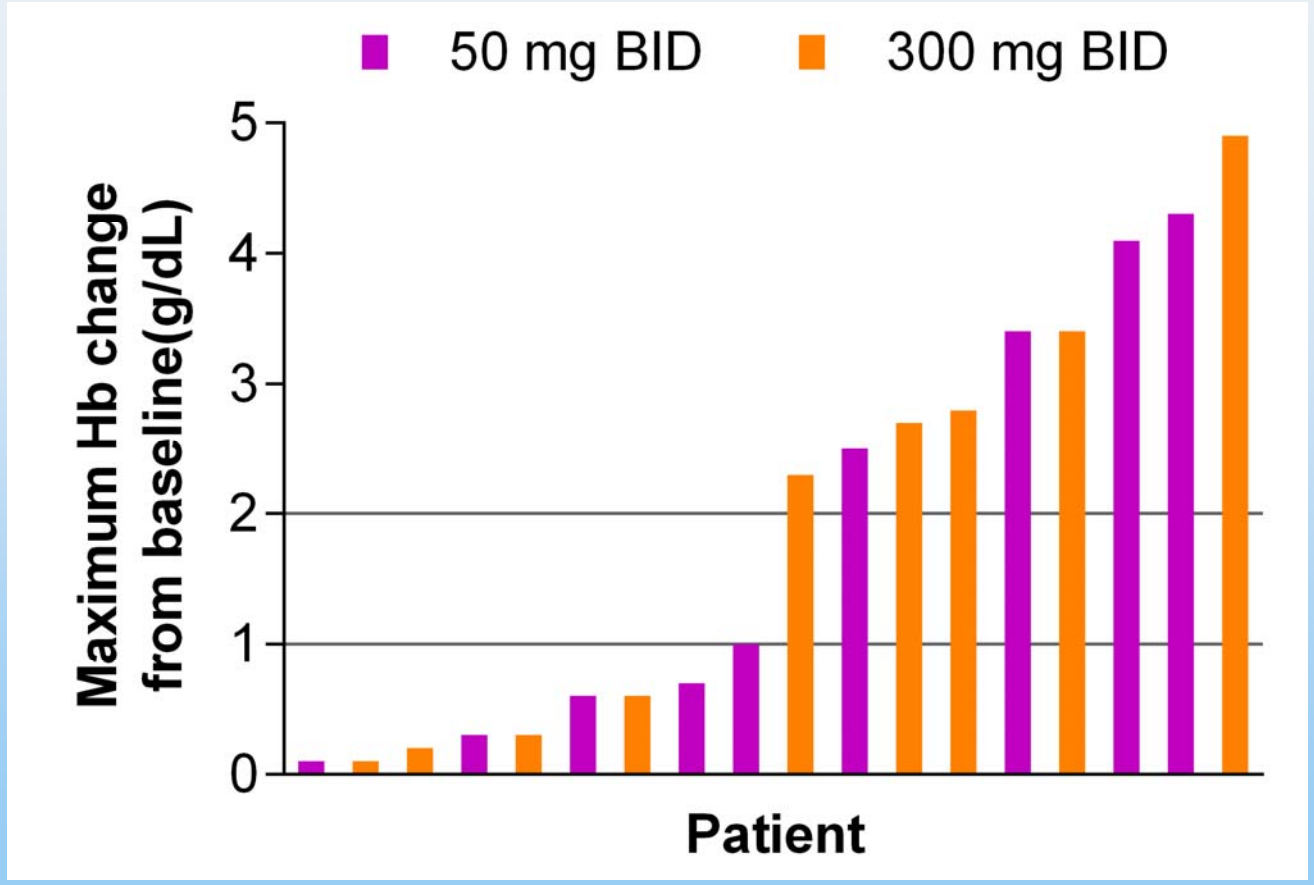


Normal reference low and high limits for men shown as horizontal dotted lines

Clinical Activity Results

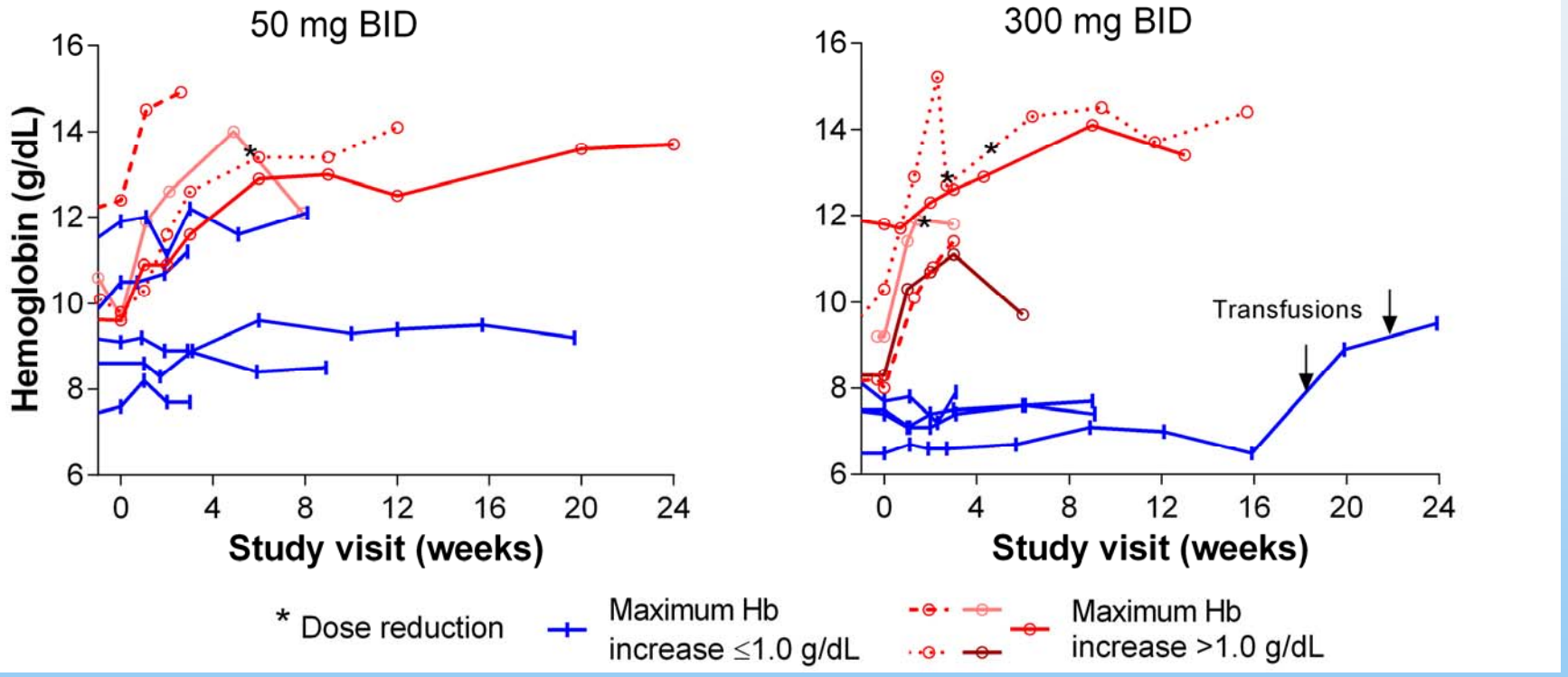
Maximum change in hemoglobin (Hb) in the 50 and 300 mg BID dose groups

- 9 of 18 patients had an increase in Hb >1.0 g/dL



Hb increases are rapid and sustained

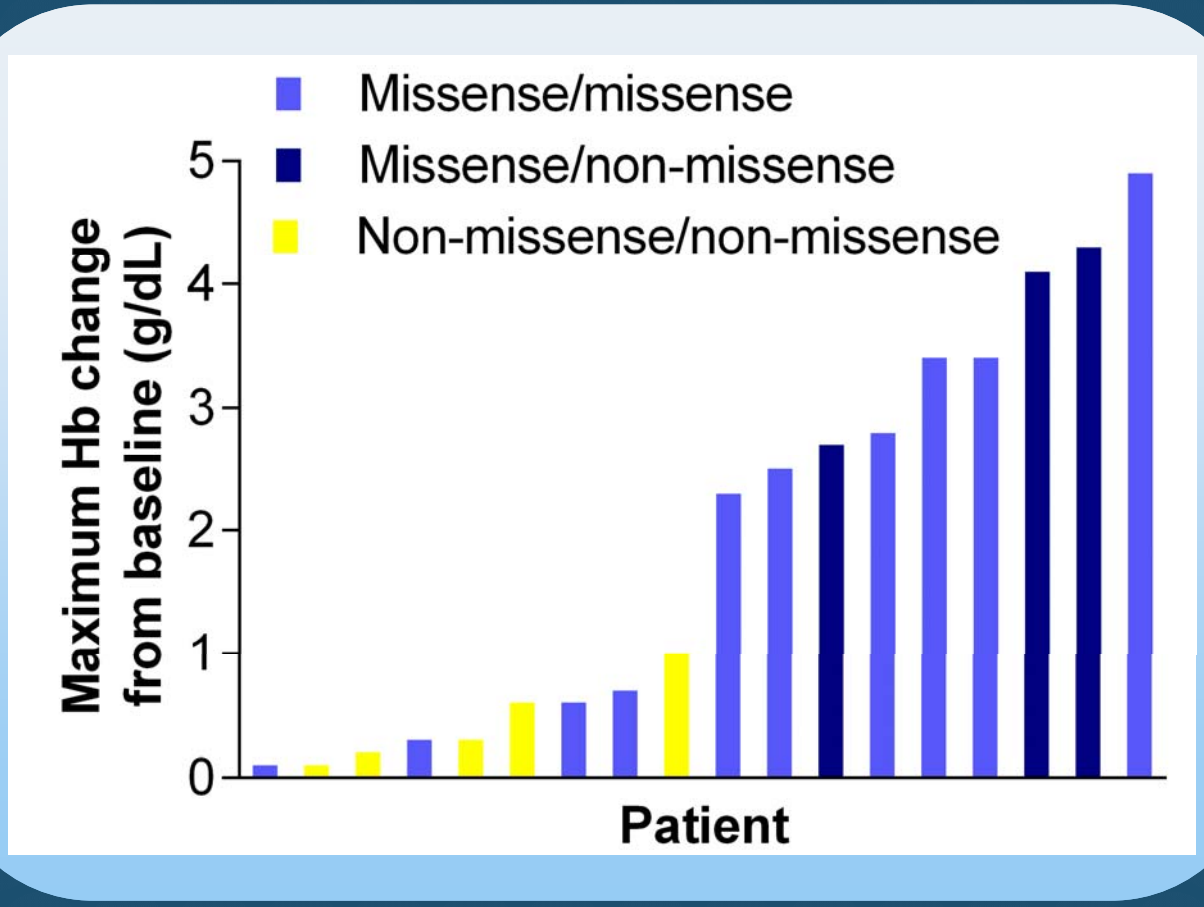
- Median time to a Hb increase >1.0 g/dL was 1.9 weeks (range, 1.1–9.1 weeks)
- In patients who had Hb increases >1.0 g/dL:
  - The mean maximum increase was 3.4 g/dL (range, 2.3–4.9 g/dL)



N=18, each line represents an individual patient

Genotype profile and Hb change

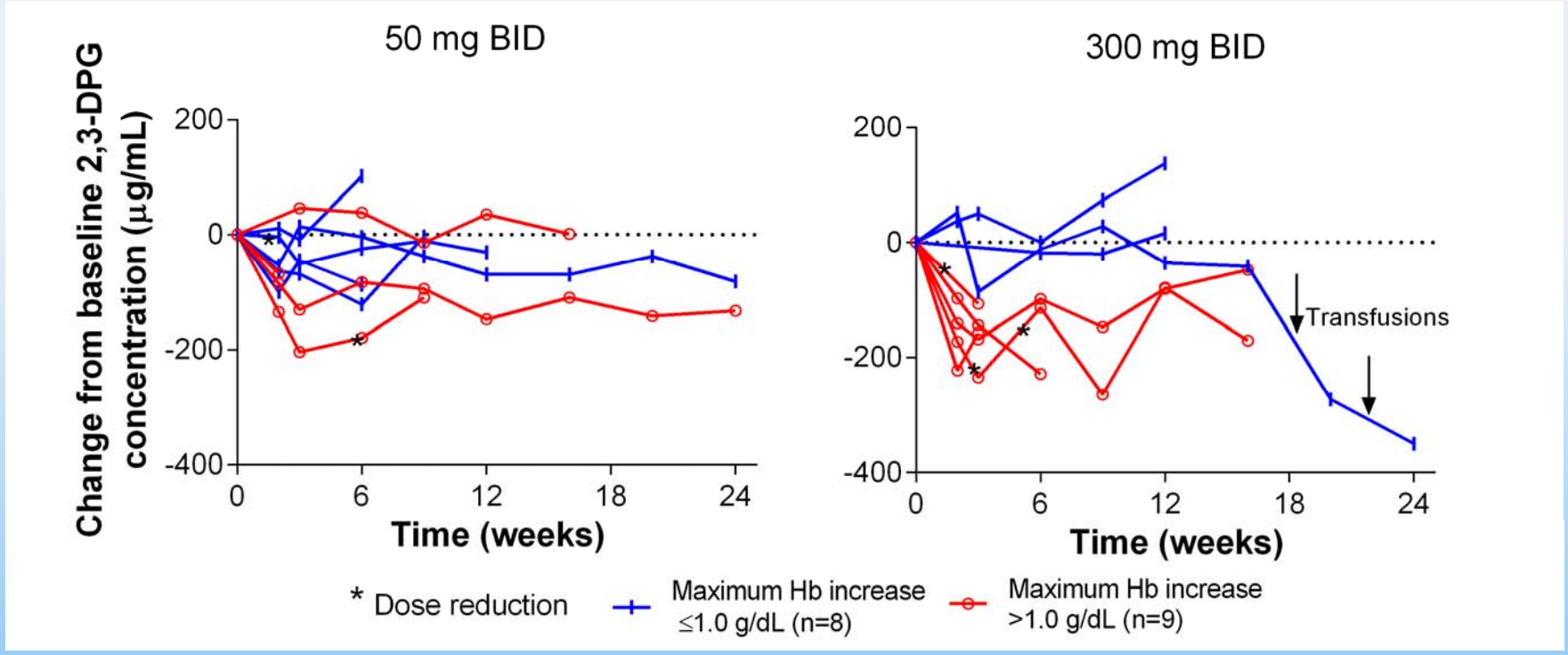
- Across all genotypes, 9 of 18 patients had an increase in Hb >1.0 g/dL
- Of 13 patients with at least one missense mutation, 9 had an increase in Hb >1.0 g/dL



Pharmacodynamic Results

Effect of AG-348 on pharmacodynamic marker 2,3-DPG

- Levels of 2,3-DPG and ATP in whole blood assessed at baseline and weeks 2, 3, 6, 9, 12, 16, 20 and 24
- No discernible effect on ATP observed
- More data are needed to clarify if any correlation exists between 2,3-DPG decreases and Hb increases >1.0 g/dL



DRIVE-PK conclusions

- AG-348 is a novel, first-in-class, PK-R activator in clinical testing as a disease-altering therapy to restore metabolic function in patients with PK deficiency
- Daily dosing with AG-348 for up to 6 months is well tolerated
- AG-348 demonstrates proof-of-concept with rapid and sustained Hb increases in patients with PK deficiency
- Preliminary genotype correlations were observed:
  - Patients with at least one missense mutation are more likely to have a Hb increase of >1.0 g/dL
  - Non-missense/non-missense genotypes have not shown increases in Hb >1.0 g/dL

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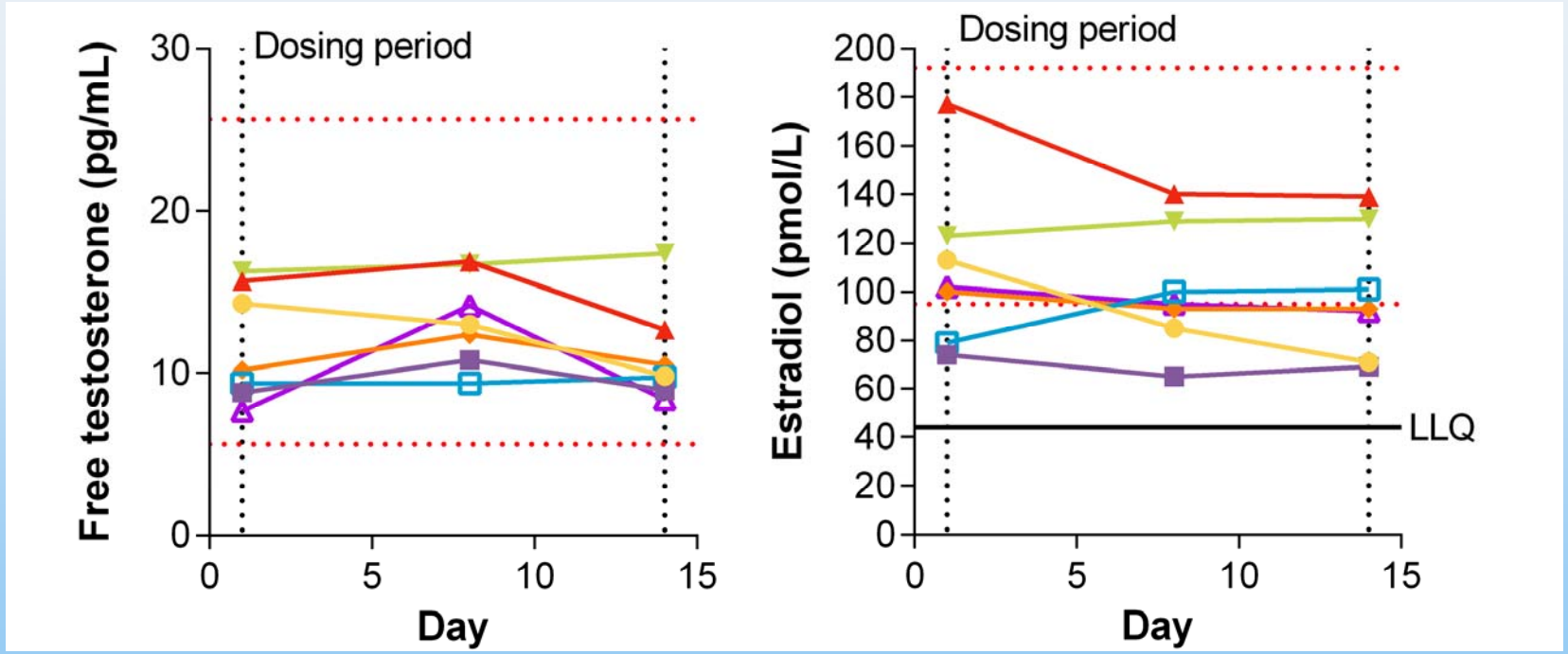
BACKUP

- AG-519 does not demonstrate off-target aromatase inhibition or effect steroid hormones



Male subjects receiving AG-519 375 mg BID. LLQ, lower limit of quantification; dotted red lines indicate reference range upper and lower limits