Effects of AG-348, a pyruvate kinase activator, in patients with pyruvate kinase deficiency: Updated results from the DRIVE PK study

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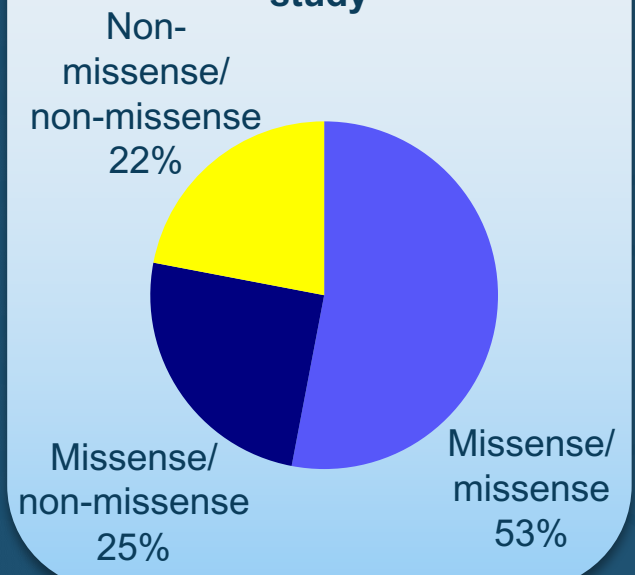
Pyruvate kinase (PK) deficiency: a severe congenital anemia

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

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

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

Extension arm

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

Fully enrolled as of November, 2016

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

Demographics

Characteristics[a]	50 mg BID, n=27	300 mg BID, n=25	Total, N=52
Men, n (%)	18 (66.7)	14 (56.0)	32 (61.5)
Age at randomization in years, median (range)	29 (18, 58)	40 (21, 62)	34 (18, 62)
Race white[b], n (%)	22 (81.5)	20 (80.0)	42 (80.8)
Hemoglobin (Hb) baseline, median (range)	9.6 (6.9, 12.3)	8.6 (6.5, 12.0)	8.9 (6.5, 12.3)
Duration of treatment, weeks, median (range)	23.0 (13.0, 76.9)	26.3 (12.9, 70.9)	24.9 (12.9,76.9)
Splenectomized, n (%)	23 (85.2)	20 (80.0)	43 (82.7)
Iron chelation prior to enrolment, n (%)	14 (51.9)	11 (44.0)	25 (48.1)
Cholecystectomy, n (%)	19 (70.4)	19 (76.0)	38 (73.1)

[a]Data cut-off March 27, 2017; [b]Not reported in 3 patients, 3 patients were Asian, and 4 were “other”

Safety summary

- AG-348 was generally well tolerated
- The majority of adverse events (AEs) were grade 1–2
- Treatment related AEs leading to discontinuation, n=3
  - Chest discomfort/pleural effusion, pharyngitis/nausea, anemia
- 13 serious AEs in 10 patients
  - Six drug-related SAEs in 5 patients: Withdrawal hemolysis followed by anemia; anemia; osteoporosis; hypertriglyceridemia; pharyngitis
    - Grade 4 hypertriglyceridemia at Week 24, resolved upon AG-348 discontinuation (Grade 1 at baseline)

Patient disposition by study period	Ongoing, N	Completed, N	Discontinued[a], N
Core	15	29[b]	8
Extension	21	0	3

[a]Reasons for discontinuation: AEs (3), investigator decision (4), and withdrew consent (4)
[b]Five subjects completing the Core period did not enter the Extension

Safety summary: Most common AEs

AEs, regardless of causality (occurring in >5 patients)	**50 mg BID n=27**		**300 mg BID n=25**		**Total N=52**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Patients experiencing at least 1 AE, n (%)	25 (92.6)	7 (25.9)	25 (100.0)	5 (20.0)	50 (96.2)	12 (23.1)
Headache	9 (33.3)	0	14 (56.0)	0	23 (44.2)	0
Insomnia	5 (18.5)	1 (3.7)	15 (60.0)	1 (4.0)	20 (38.5)	2 (3.8)
Nausea	10 (37.0)	0	9 (36.0)	0	19 (36.5)	0
Viral upper respiratory tract infection	7 (25.9)	0	2 (8.0)	0	9 (17.3)	0
Arthralgia	5 (18.5)	0	3 (12.0)	0	8 (15.4)	0
Fatigue	4 (14.8)	0	4 (16.0)	0	8 (15.4)	0
Back pain	4 (14.8)	0	3 (12.0)	0	7 (13.5)	0
Cough	4 (14.8)	0	3 (12.0)	0	7 (13.5)	0
Dizziness	4 (14.8)	0	3 (12.0)	1 (4.0)	7 (13.5)	1 (1.9)
Vomiting	3 (11.1)	0	4 (16.0)	0	7 (13.5)	0
Hot flush	1 (3.7)	0	6 (24.0)	0	7 (13.5)	0
Diarrhea	3 (11.1)	0	3 (12.0)	0	6 (11.5)	0
Influenza	5 (18.5)	1 (3.7)	1 (4.0)	0	6 (11.5)	1 (1.9)

Grade 3 AEs not reported in previous slide or table above: colitis (n=1), thrombosis (n=1), pharyngitis (n=1), post procedural hemorrhage (n=1), hypertension (n=1)

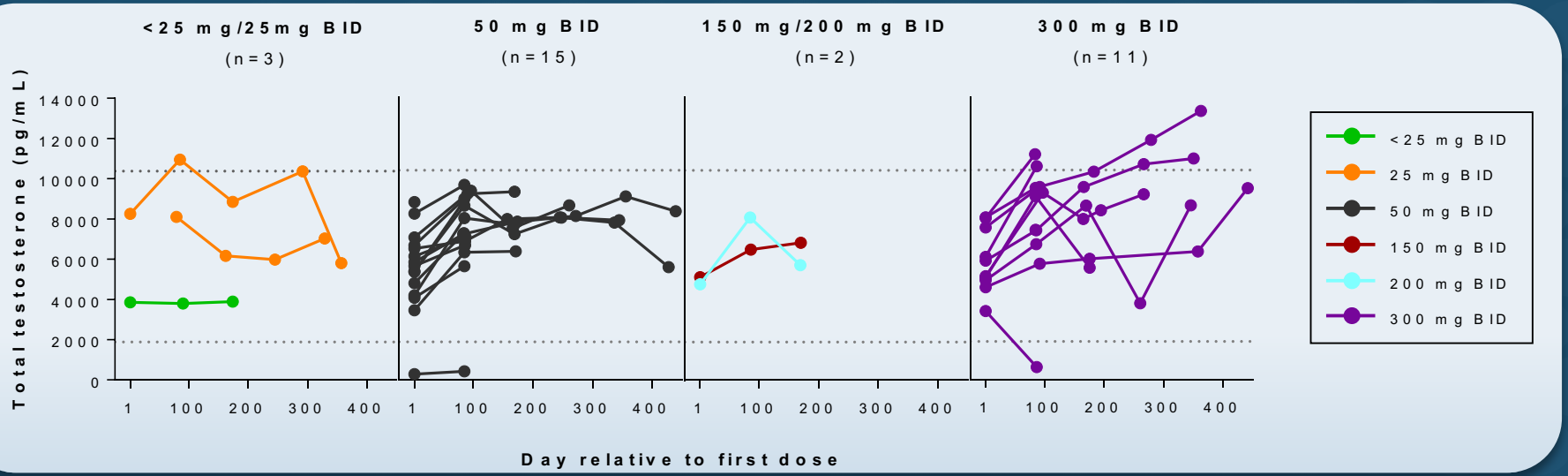
AEs graded using National Cancer Institute Common Terminology Criteria, version 4.03

Dose titration in DRIVE PK

- Patients randomized to 50 mg or 300 mg BID AG-348 starting dose
  - Dose decreased:
    - AEs (e.g. insomnia)
    - Hb exceeding midpoint of normal range (Male: Hb >15.0 g/dL; Female>13.5 g/dL)
  - Dose increased:
    - Lack of Hb response
- Range of doses (5 mg QD–300 mg BID) used
- Efficacy and steroid hormone levels analyzed by the dose received for the longest duration in the Core period

Effect of AG-348 on hormones: total testosterone in men

- Preliminary findings are consistent with aromatase inhibition by AG-348 across multiple dose levels in men
  - Most testosterone values remained within the normal range
  - DEXA scan data inconclusive
  - Longer follow up required to assess clinical impact

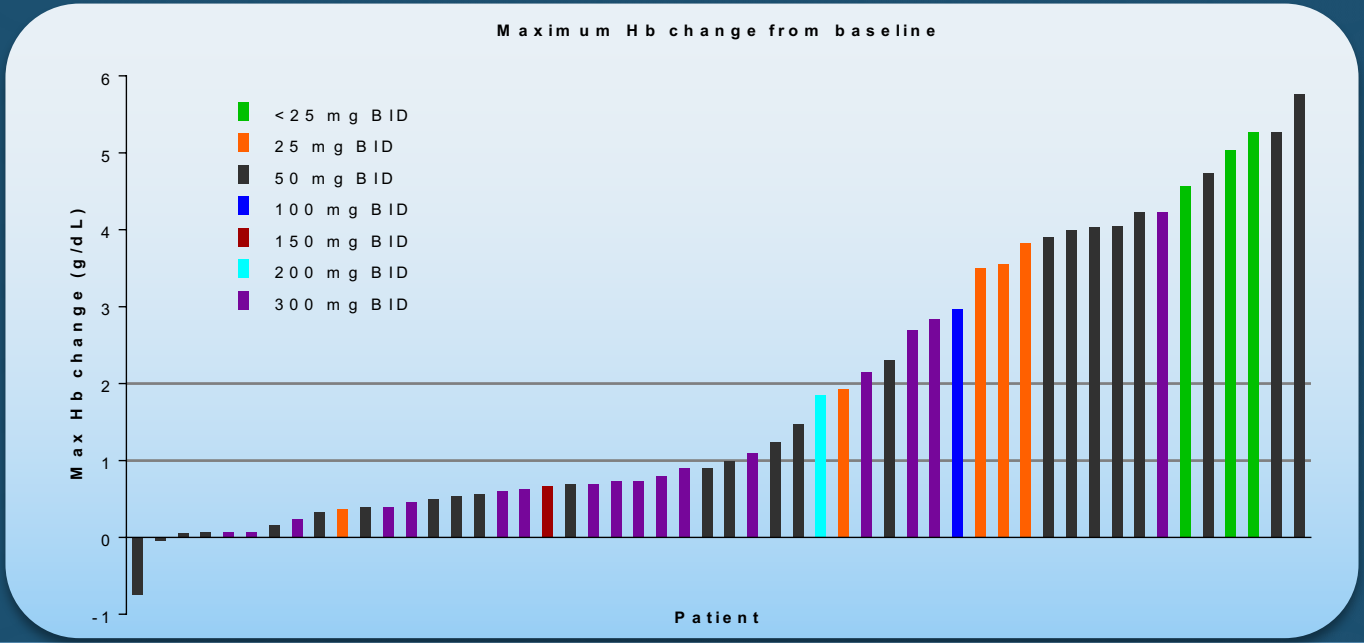


Normal reference low and high limits shown as horizontal dotted lines; DEXA = dual energy X-ray absorptiometry

Clinical activity results

Maximum Hb increase observed during the Core period

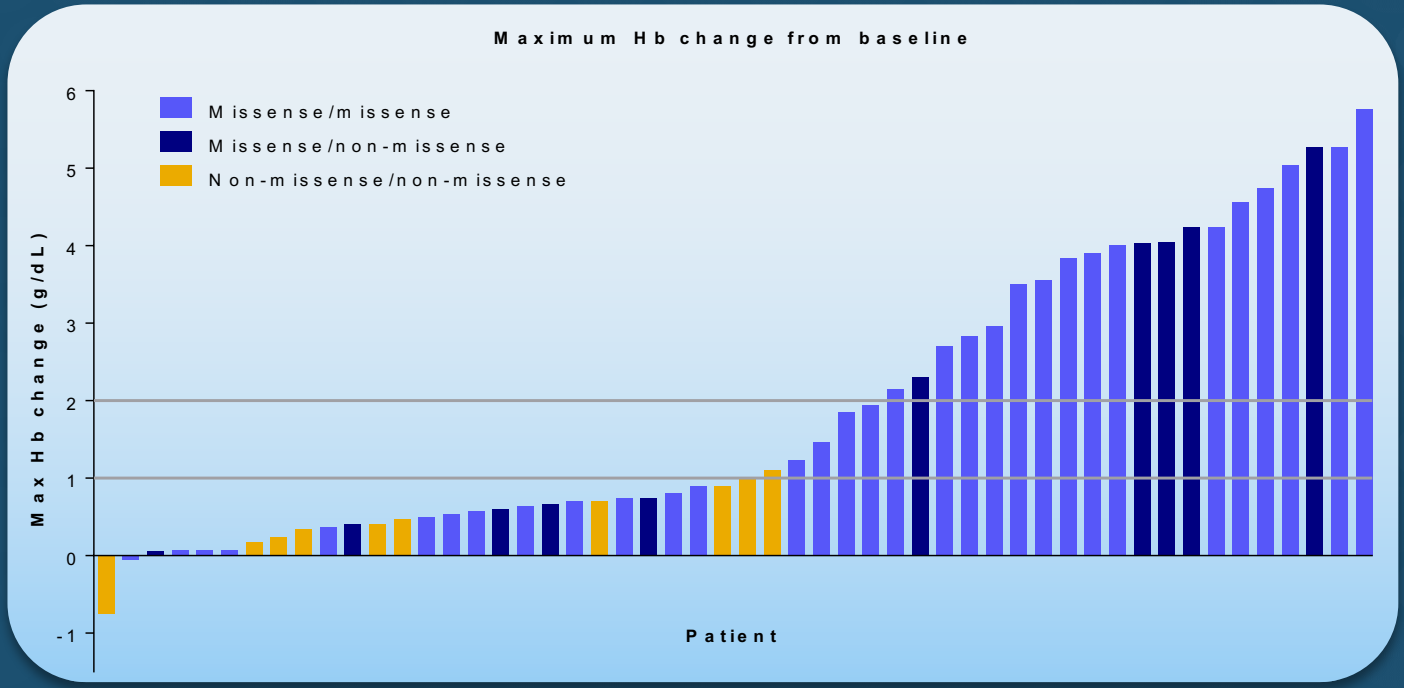
- 25/52 (48%) patients had a maximum Hb increase of >1.0 g/dL
  - The mean maximum increase was 3.5 g/dL (range 1.1-5.8 g/dL)



The baseline value is the average of all central assessments within the screening period (42 days prior to Day 1)

Maximum Hb increase observed by genotype

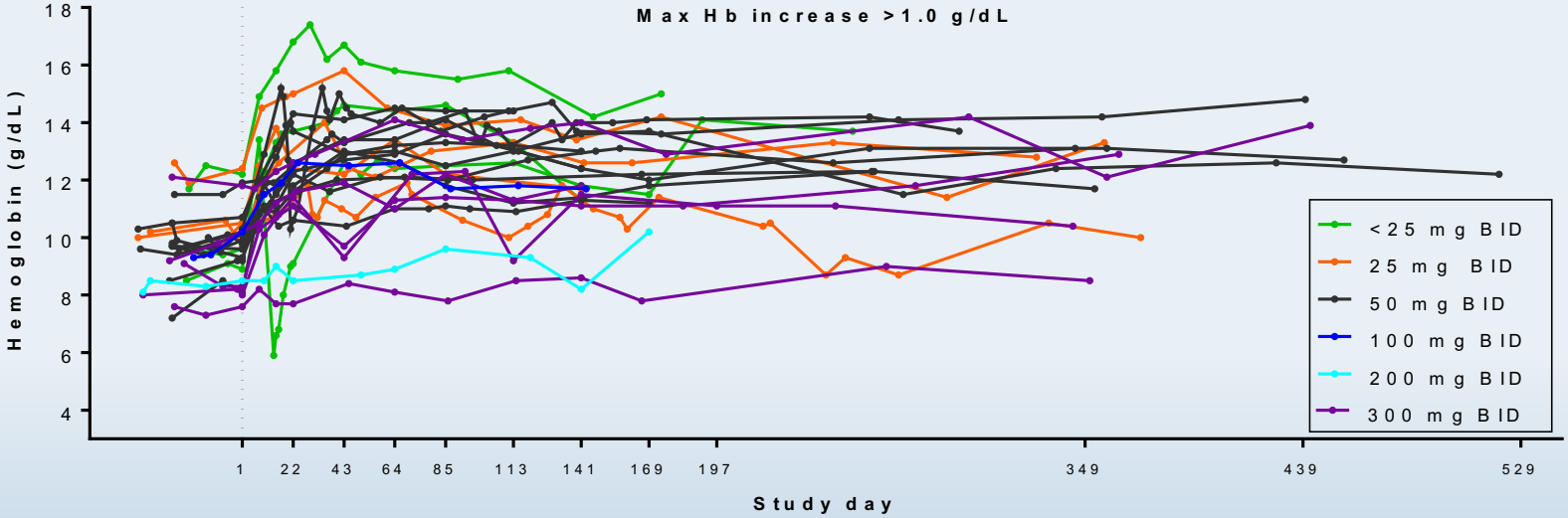
- 25/52 (48%) patients had a max increase in Hb >1.0 g/dL
  - 24/42 (57%) patients who had ≥1 missense mutation had Hb increase >1.0 g/dL



The baseline value is the average of all central assessments within the screening period (42 days prior to Day 1)

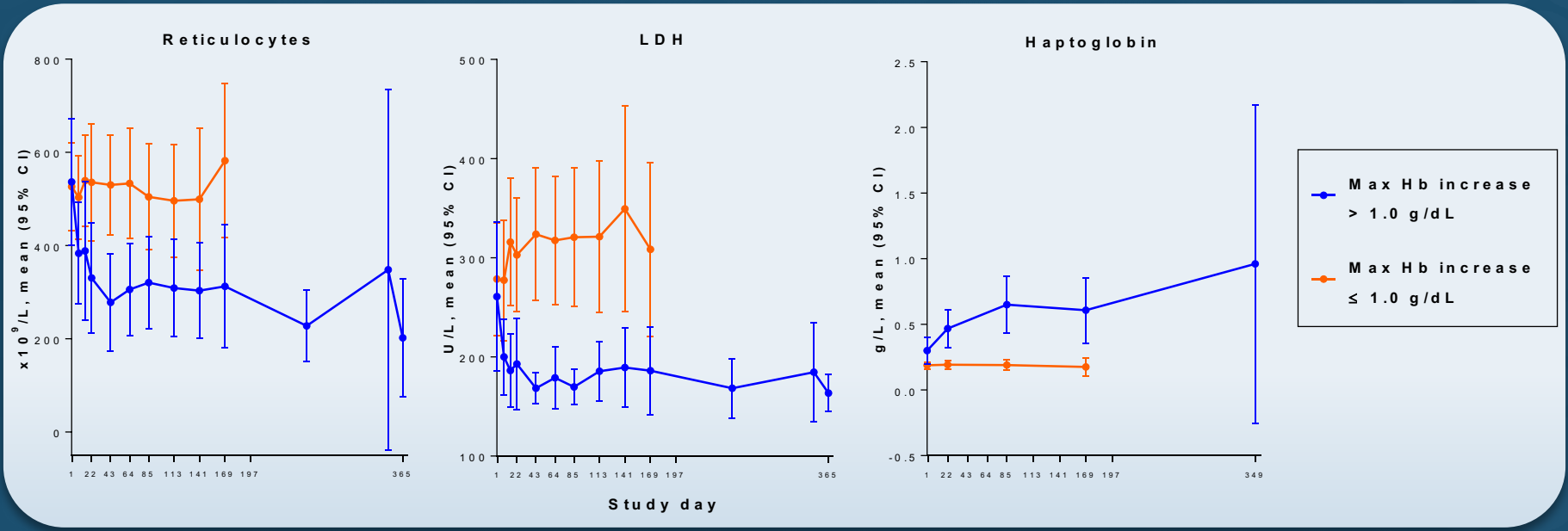
Majority of Hb increases are rapid and sustained

- Median time to the first observation of a Hb increase >1.0 g/dL above baseline was 10 days (range 7–141 days)
  - Median baseline Hb in subjects who experienced a maximum Hb increase of >1.0 g/dL was 9.7 g/dL (range 7.5–12.3 g/dL) vs. 8.0 g/dL (range 6.5–10.1) in subjects who did not
- In 8 patients, the dose had to be held or reduced due to rapid rise in Hb



Hemolysis markers improve in patients with Hb increase of >1.0 g/dL

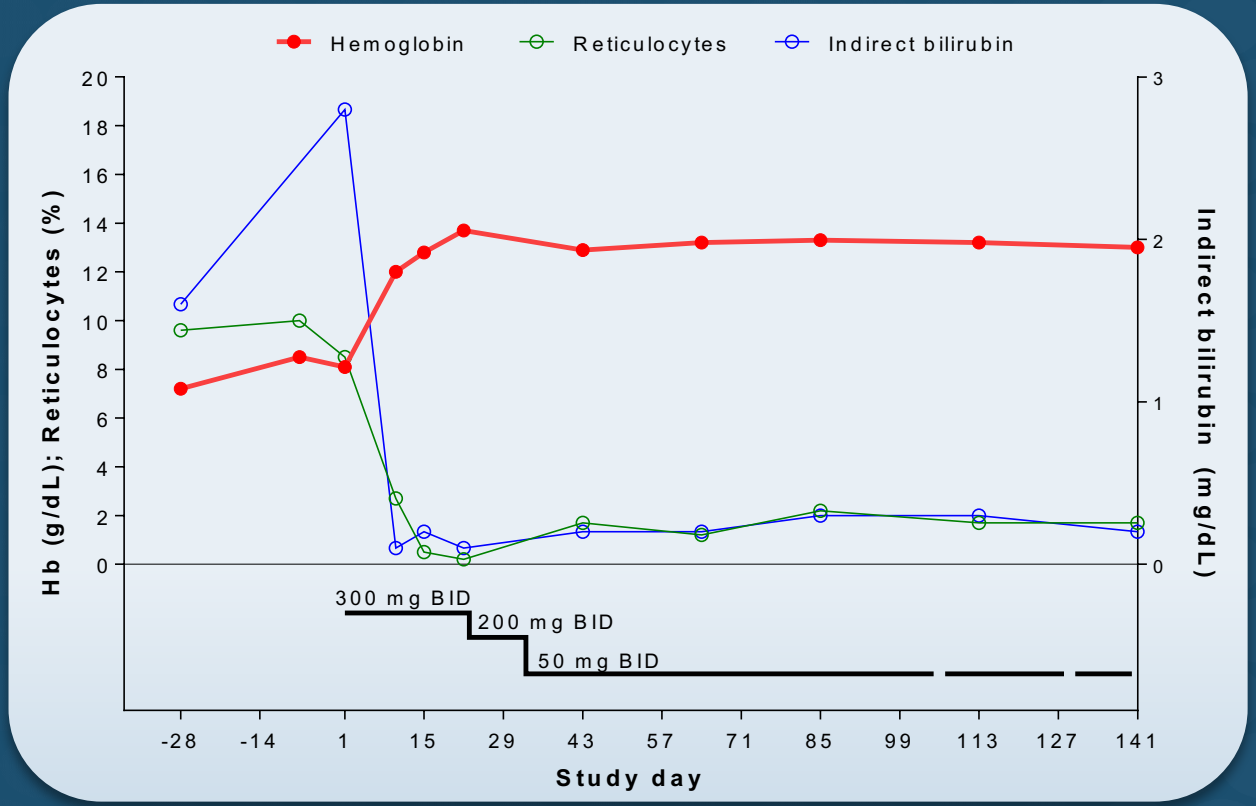
- Rapid decreases in reticulocytes and LDH in the first weeks of dosing
- Steady increase in haptoglobin



Only visits with ≥5 subjects included. Figure shows central laboratory results. LDH = lactate dehydrogenase

Hb response with improvements in hemolysis parameters: Single subject experience with AG-348

- 35 yo female, white, missense/missense genotype (T384M/R479H)



DRIVE-PK conclusions

- AG-348 is a novel, first-in-class PK-R activator in clinical testing as a potential disease-altering therapy for patients with PK deficiency
- Chronic daily dosing with AG-348 is well tolerated
  - Clinical significance of AG-348 aromatase inhibition is unclear
  - One grade 4 serious AE of elevated triglycerides was observed
- 25 of 52 (48%) subjects had a maximum Hb increase of >1.0 g/dL
  - Responses are rapid in onset and durable
  - Other parameters (reticulocytes, LDH and haptoglobin) indicate decreased hemolysis in responders
  - Some genotype–Hb response correlations were observed
- These data highlight the potential of AG-348 as the first disease-altering treatment for patients with PK deficiency, providing rationale for pivotal studies

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