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

Rachael F Grace[1], **D Mark Layton[2]**, Frédéric Galactéros[3], Christian Rose[4], Wilma Barcellini[5], D Holmes Morton[6], Eduard van Beers[7], Hassan Yaish[8], Yaddanapudi Ravindranath[9], Kevin HM Kuo[10], Sujit Sheth[11], Janet L Kwiatkowski[12], Bruce Silver[13], Charles Kung[14], Marvin Cohen[15], Hua Yang[14], Penelope A Kosinski[14], Lei Hua[14], Ann Barbier[14], Bertil Glader [16]

[1]Dana-Farber Boston Children's Cancer and Blood Disorders Center, Boston, MA USA; [2]Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; [3]Unité des Maladies Génétiques du Globule Rouge, CHU Henri Mondor, Créteil, France; [4]Hôpital Saint Vincent de Paul, Lille, France; [5]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [6]Central Pennsylvania Clinic, Belleville, PA, USA; [7]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands; [8]University of Utah, Salt Lake City, UT, USA; [9]Wayne State University School of Medicine, Children's Hospital of Michigan, Detroit, MI, USA; [10]University of Toronto, Toronto, Canada; [11]Weill Cornell Medical College, New York, NY, USA; [12]Children's Hospital of Philadelphia and Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA; [13]Bruce A Silver Clinical Science and Development, Dunkirk, MD, USA; [14]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [15] MBC Pharma Solutions, Newtown, PA, USA; [16]Stanford University School of Medicine, Palo Alto, CA, USA

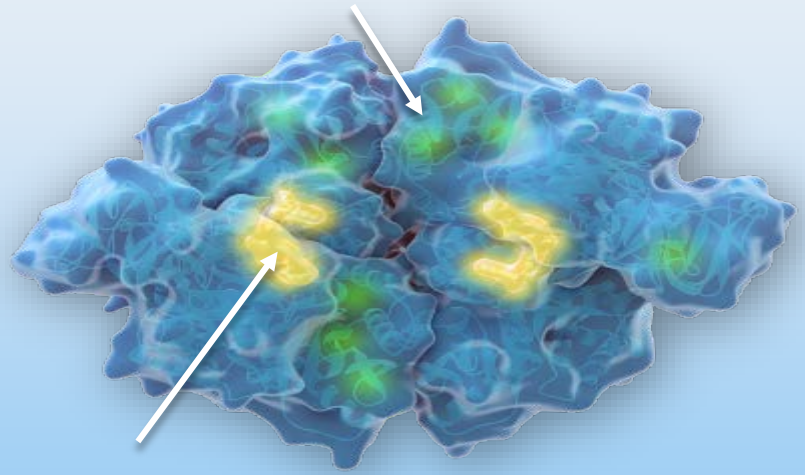
Presented at the British Blood Transfusion Society Red Cell Special Interest Group, 13 September 2017

Disclosures

- This study was funded by Agios Pharmaceuticals Inc.
- Rachael F Grace: Agios – study co-principal investigator and scientific advisor
- D Mark Layton: Agios – study investigator
- Frédéric Galactéros – study investigator
- Christian Rose: Agios – study investigator
- Wilma Barcellini: Agios – study investigator, no other disclosures
- D Holmes Morton – study investigator
- Eduard van Beers – study investigator
- Hassan Yaish – study investigator
- Yaddanapudi Ravindranath – study investigator
- Kevin HM Kuo – study investigator
- Sujit Sheth – study investigator
- Janet L Kwiatkowski: Agios – study investigator; Agios, Shire, Sideris, and Ionis Pharmaceuticals – consultant
- Bruce Silver, Marvin Cohen: Agios – consultants
- Bertil Glader: Agios – study co-principal investigator and scientific advisor
- Charles Kung, Hua Yang, Penelope A Kosinski, Lei Hua, Ann J Barbier: Agios – employees and stockholders
- Editorial assistance was provided by Christine Ingleby, PhD, Excel Scientific Solutions, Horsham, UK, and supported by Agios

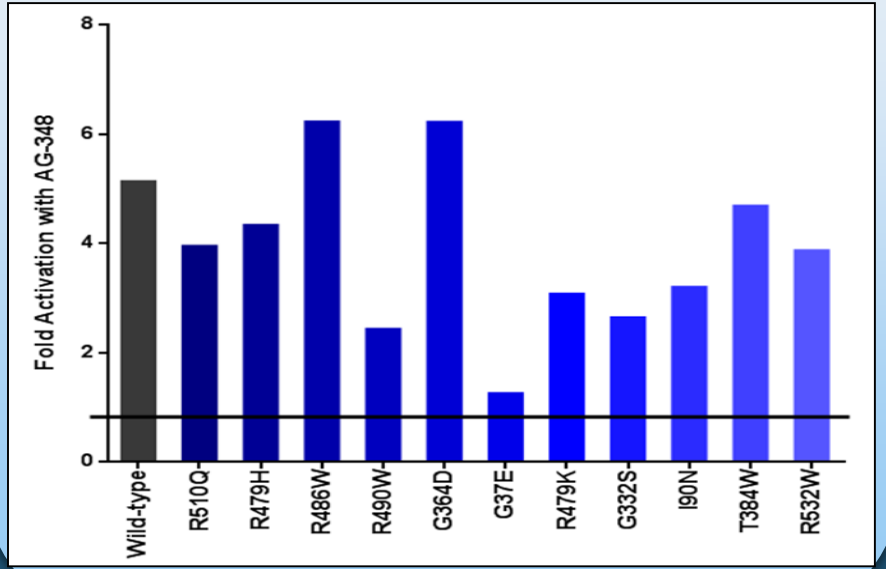
AG-348: allosteric activator of wild-type and mutant PK-R

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



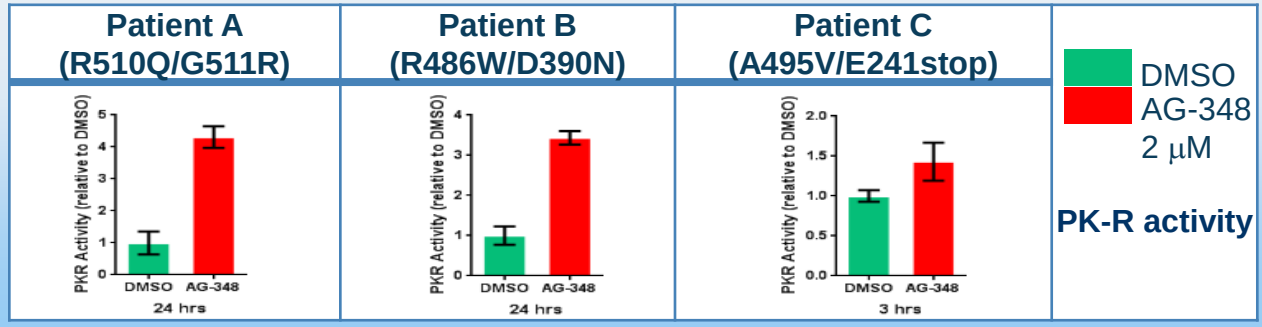
AG-348 (yellow) binds at the PK-R dimer-dimer interface, away from the active site and the most common mutations

AG-348 potently activates recombinant PK-R wild type and nearly all mutant enzymes tested *in vitro*

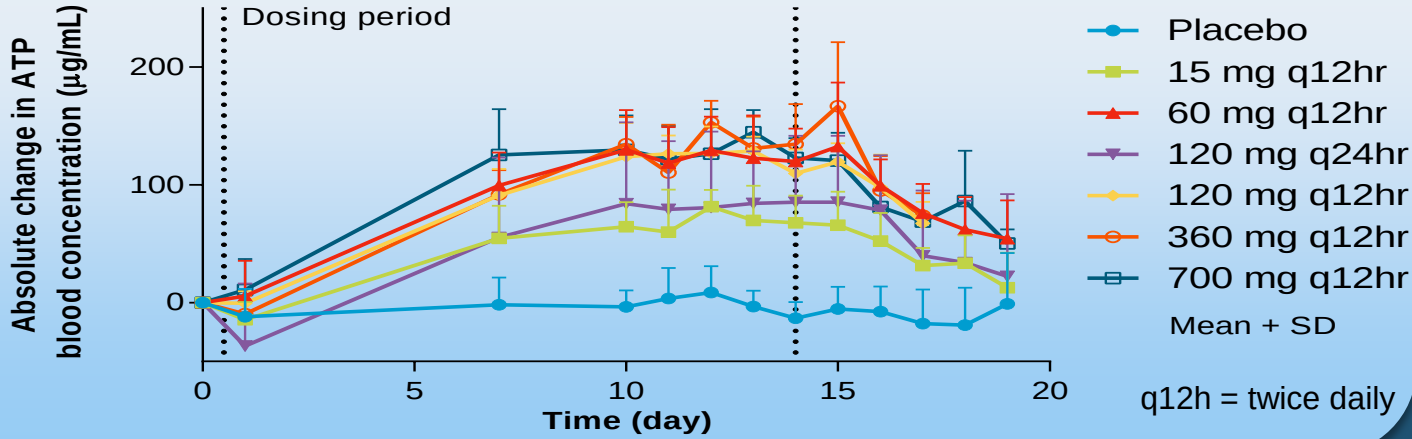


AG-348 activates the glycolytic pathway

PK deficient patient red blood cell samples



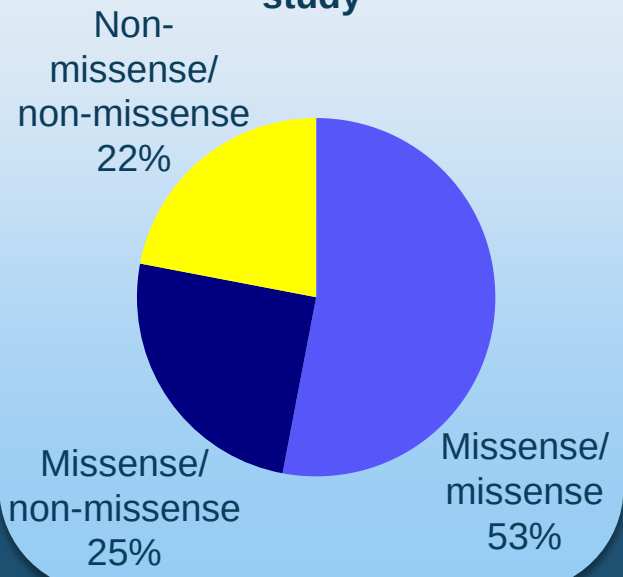
ATP levels in healthy volunteers given AG-348 for 14 days



Pyruvate kinase (PK) deficiency: a severe congenital anaemia

Description	• Presents in childhood with severe haemolytic anaemia
Aetiology	• Caused by mutations in the *PK-LR* gene coding for erythrocyte pyruvate kinase (PK-R)
Disease burden	• Lifelong haemolytic anaemia • 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**: haemoglobin, reticulocyte count, other haematological 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. 2,3-DPG = 2,3 diphosphoglycerate; 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)
Haemoglobin (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, anaemia
- 13 serious AEs in 10 patients
  - Six drug-related SAEs in 5 patients: Withdrawal haemolysis followed by anaemia; anaemia; osteoporosis; hypertriglyceridaemia; pharyngitis
    - Grade 4 hypertriglyceridaemia 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

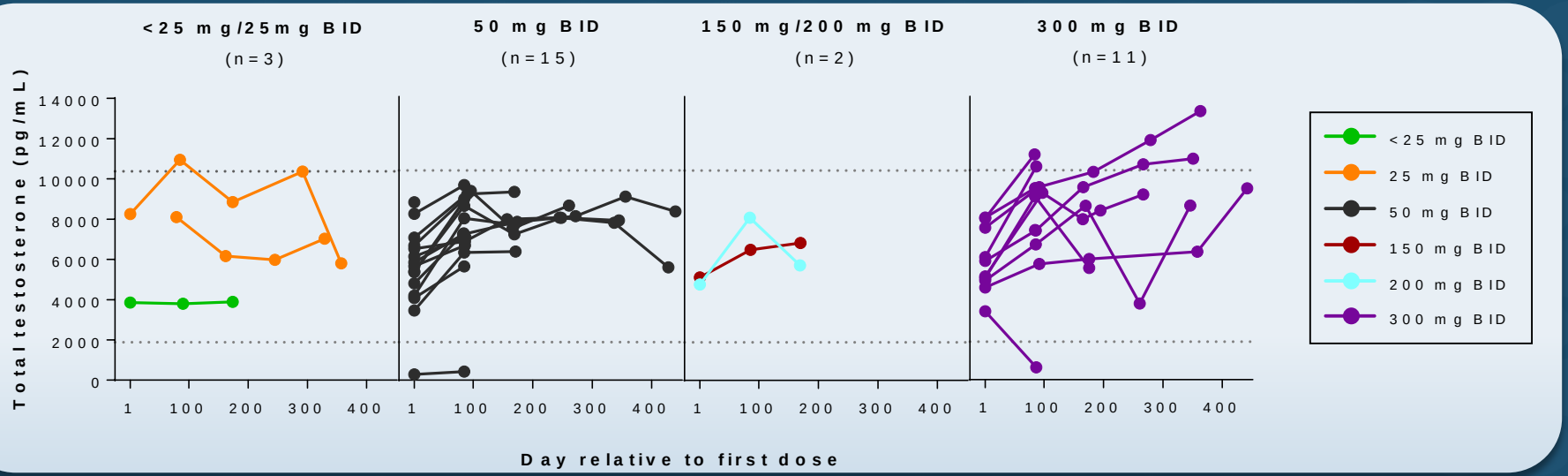
Dose titration in DRIVE PK

- Patients randomized to starting dose of 50 mg or 300 mg BID AG-348
  - Dose decreased:
    - AEs (e.g. insomnia)
    - Hb exceeding midpoint of normal range (Male: >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

QD = once daily

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

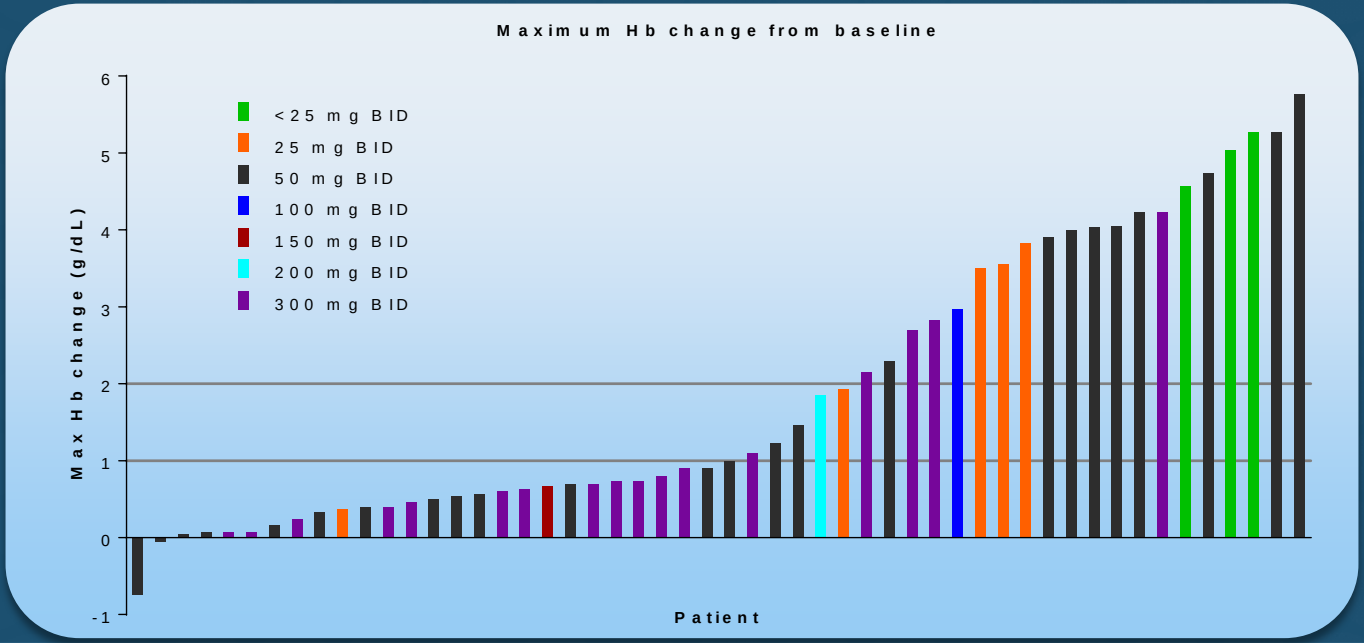


Normal reference low and high limits shown as horizontal dotted lines; DEXA = dual energy X-ray absorptiometry

Clinical activity results

Maximum Hb increase observed during the Core period

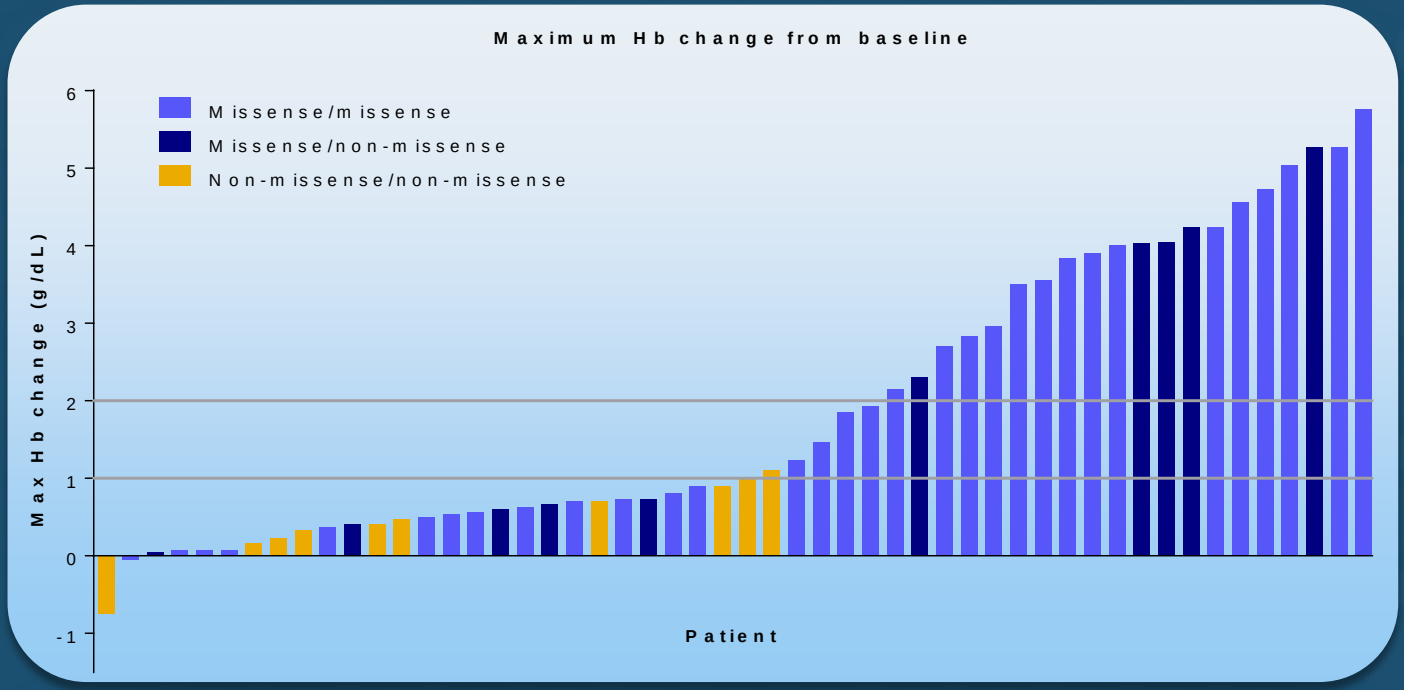
- 25/52 (48%) patients had a maximum Hb increase of >1.0 g/dL
  - The mean maximum increase was 3.5 g/dL (range 1.1–5.8 g/dL)



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

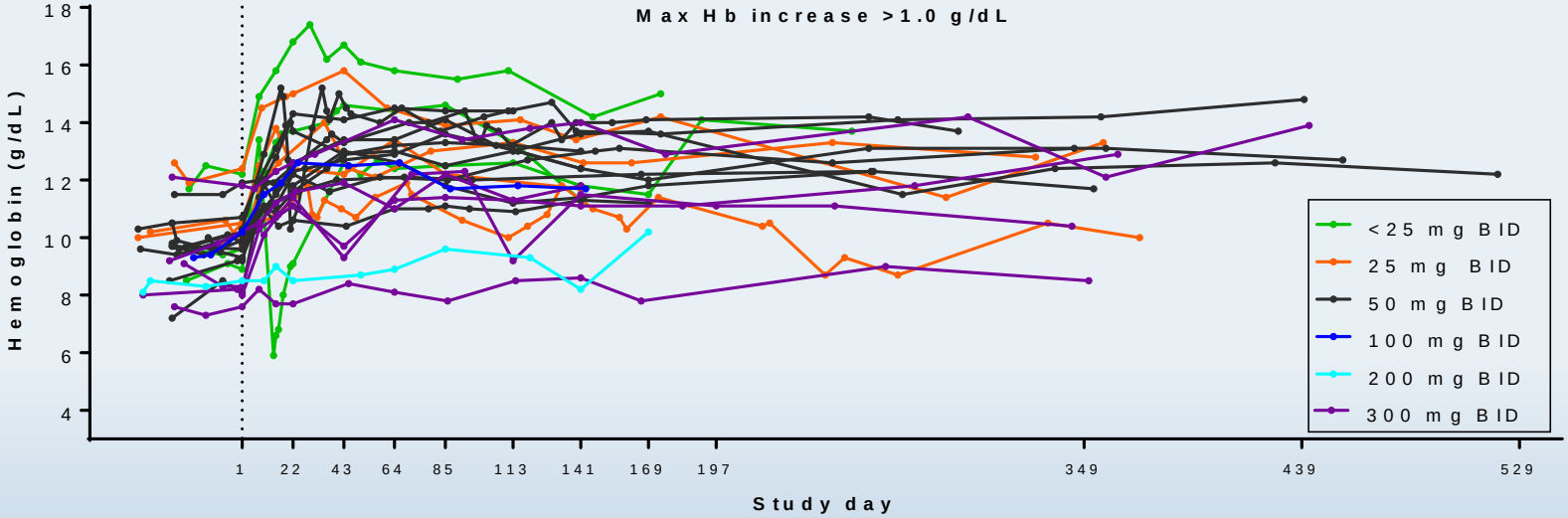
- 25/52 (48%) patients had a maximum increase in Hb >1.0 g/dL
  - 24/42 (57%) patients who had ≥1 missense mutation had Hb increase >1.0 g/dL



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

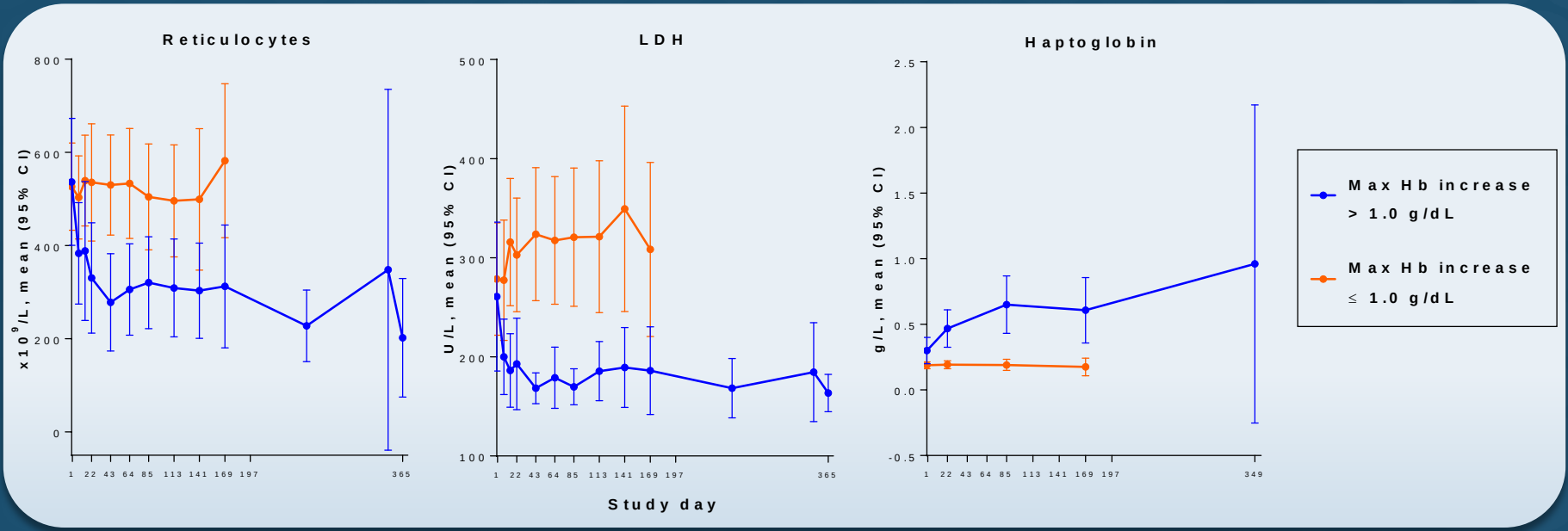
Majority of Hb increases are rapid and sustained

- Median time to the first observation of an 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



Haemolysis markers improved in patients with Hb increase of >1.0 g/dL

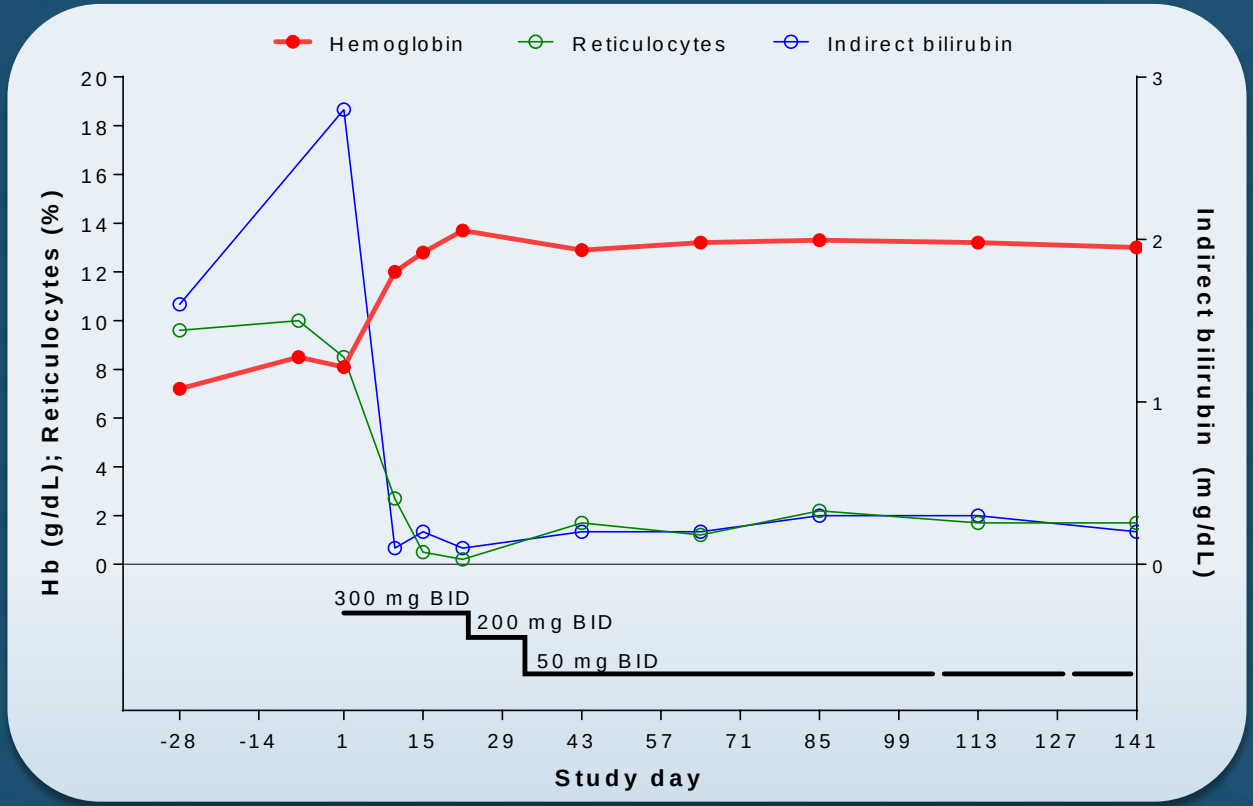
- Rapid decreases in reticulocytes and LDH in the first weeks of dosing
- Steady increase in haptoglobin



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

Hb response with improvements in haemolysis parameters: single subject experience with AG-348

- Female 35 years of age, 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 haemolysis in responders
  - Some genotype–Hb response correlations were observed
- These data highlight the potential of AG-348 to be the first disease-altering treatment for patients with PK deficiency, providing a rationale for pivotal studies

Acknowledgments

- We would like to thank the patients who agreed to participate in this study
- We would also like to thank all the clinical research sites and study investigators:
  - Boston Children's Hospital; Rachael F Grace
  - Stanford University Medical Centre; Bertil Glader
  - University of Utah; Hassan Yaish
  - Weill Cornell – New York Presbyterian Hospital; Sujit Sheth
  - The Children's Hospital of Philadelphia; Janet L Kwiatkowski
  - Central Pennsylvania Clinic; D Holmes Morton
  - Wayne State University School of Medicine; Yaddanapudi Ravindranath
  - University of Toronto – University Health Network; Kevin HM Kuo
  - Hammersmith Hospital; D Mark Layton
  - Universitair Medisch Centrum Utrecht; Eduard van Beers
  - Hôpital Henri Mondor; Frédéric Galactéros
  - Hôpital Saint Vincent de Paul; Christian Rose
  - Hôpital de la Timone; Emmanuelle Bernit
  - Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico; Wilma Barcellini
- We would like to thank Drs Ellis Neufeld and David Nathan for helpful discussions
- This clinical study was funded by Agios Pharmaceuticals

Editorial support was provided by Christine Ingleby, PhD, Excel Scientific Solutions, Horsham, UK, and supported by Agios