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Mitapivat (AG-348) long-term safety and efficacy in pyruvate kinase deficiency: 3-year results of the DRIVE-PK study

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BACKGROUND

- Pyruvate kinase (PK) deficiency is an under-recognized autosomal recessive disease caused by mutations in the *PKLR* gene
- Pathogenic mutations lead to reduced activity of PKR, the red blood cell–specific PK enzyme, which results in lifelong hemolytic anemia[1,2]
- Acute and chronic complications of supportive care (eg, transfusions, splenectomy, or iron chelation) can additionally burden patients with PK deficiency
- Mitapivat (AG-348)—an oral, small-molecule, allosteric activator of both wild-type and mutant PKR[3,4]—is undergoing clinical evaluation in patients with PK deficiency
- DRIVE-PK is a phase 2, randomized, open-label, dose-ranging study of mitapivat in adults with PK deficiency who were not regularly receiving red cell transfusions. Results from the first 6 months of the study showed:
  - A rapid increase from baseline of > 1.0 g/dL in hemoglobin (Hb) levels in 50% of patients
  - An acceptable safety profile[5]

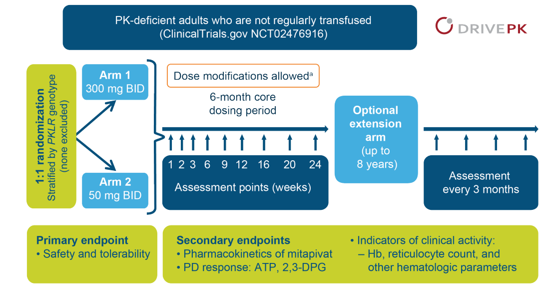
OBJECTIVE

- To report long-term safety and efficacy of mitapivat in patients with PK deficiency continuing in the extension period of DRIVE-PK (ClinicalTrials.gov NCT02476916)

METHODS

- DRIVE-PK is a global study, with patients enrolled at 14 centers in the US, Canada, and Europe
- Patients who experienced clinical benefit without any concerning safety issues related to mitapivat (investigator discretion) could opt to enter the extension period (**Figure 1**)

Figure 1. Study design



Not regularly transfused = no more than 3 units of red blood cells transfused in the 12 months prior to the first day of study dosing and no transfusions within 4 months of the first day of study dosing
All patients provided written informed consent
[a]Dose adjustments were allowed in the core period on the basis of safety, side-effect profile, and Hb response
2,3-DPG = 2,3-diphosphoglycerate; ATP = adenosine triphosphate; BID = twice daily; PD = pharmacodynamic

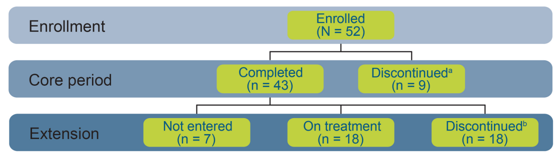
METHODS (CONTINUED)

- Protocol amendments during the extension period required that:
  - Patients who did not have an increase from baseline Hb of ≥ 1.0 g/dL for ≥ 3 of the 4 prior measurements withdraw from the study
  - Patients treated with mitapivat doses > 25 mg BID undergo a dose taper and continue on a dose that maintained their Hb level at no lower than 1.0 g/dL below their pretaper Hb level

Disposition

- Of the 52 patients enrolled in the study, 43 completed the core period (24 weeks) and 18 remained in the study as of 27March2019 (**Figure 2**)

Figure 2. Enrollment and patient disposition during the core period and the extension phase



[a]Adverse events (AEs), n = 4 (pharyngitis and nausea, hemolytic anemia, hypertriglyceridemia, and pleural effusion); investigator decision, n = 2; patient withdrew consent, n = 3
[b]Investigator decision, n = 7; other reasons, n = 7; patient withdrew consent, n = 1; AEs, n = 2 (elevated alanine aminotransferase and nonalcoholic steatohepatitis, and renal cell carcinoma); noncompliance, n = 1

RESULTS

Treatment

- Among the 18 patients continuing in the extension period, the last post-taper mitapivat doses were:
  - ≤ 25 mg BID (excluding missed doses; n = 12)
  - 50 mg BID (n = 5)
  - 200 mg BID (n = 1)
- Median (range) duration of treatment was 35.6 (28.7−41.9) months

Table 1. Demographic characteristics of all patients and those who continued in the extension period

Characteristic	Total N = 52	Continued n = 18
Male, n (%)	32 (61.5)	10 (55.6)
Age at screening, median (range), years	34 (18–61)	33.5 (19–61)
White, n (%)	43 (82.7)	17 (94.4)
Hb baseline, median (range), g/dL	8.9 (6.5–12.3)	9.7 (7.9–12.0)
Splenectomy, n (%)	43 (82.7)	11 (61.1)
Cholecystectomy, n (%)	38 (73.1)	14 (77.8)
Iron chelation prior to enrollment, n (%)	25 (48.1)	5 (27.8)
Osteoporosis, n (%)	8 (15.4)	2 (11.1)
Mutation category, n (%)		
Missense/missense	32 (61.5)	14 (77.8)
Missense/non-missense	10 (19.2)	4 (22.2)
Non-missense/non-missense	10 (19.2)	0 (0)

RESULTS (CONTINUED)

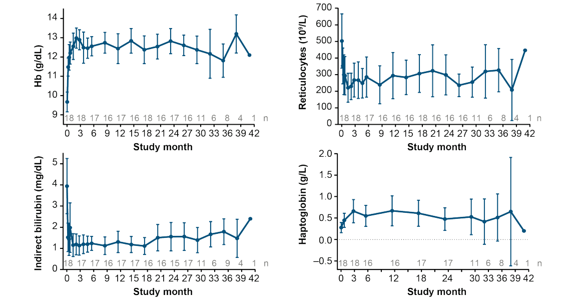
Baseline characteristics

- No differences in age, race, or sex were observed between patients who continued in the extension period and those in the total cohort (**Table 1**)
- Patients continuing treatment had a lower splenectomy rate, and fewer had received prior iron chelation therapy
- The baseline Hb range of patients who continued in the extension period overlapped with the baseline range of the total cohort
- All continuing patients had at least one missense *PKLR* mutation, compared with 81% of patients originally enrolled

Efficacy

- Improvements in Hb and other markers of hemolysis, including reticulocytes, indirect bilirubin, and haptoglobin, achieved during the core period were sustained during the extension period (up to 42 months) (**Figure 3**)

Figure 3. Hematologic responses for the patients who continued in the extension period



Data are presented as mean ± 95% CI

Safety

- Mitapivat was generally well tolerated; the majority of AEs were grade 1–2
- AEs for patients who continued in the study (n = 18) were comparable in the core and extension periods (**Table 2**)
  - Headache, insomnia, fatigue, and nasopharyngitis were the most commonly reported AEs in the extension period
  - Fewer patients reported nausea and hot flush in the extension period than in the core period (2 vs 6 and 0 vs 5, respectively)
  - More patients reported nasopharyngitis in the extension period than in the core period (5 vs 1)
  - No new safety signals were identified in the extension period
- Ten patients had an increase from baseline of one grade or more in either aspartate transaminase or alanine aminotransferase on the basis of their worst grade
- Ten patients had an increase from baseline of one grade or more in triglycerides on the basis of their worst grade
- Male subjects experienced an increase in total and free testosterone and a decrease in estradiol and estrone consistent with previously reported mild off-target aromatase inhibition. Testosterone levels have been observed to remain in the normal range for the majority of subjects treated with mitapivat
- In a subset of patients where bone mineral density (femoral neck, total hip, and total lumbar spine) was analysed, no clinically meaningful trends were evident

Table 2. Most common AEs in patients who continued in the extension period[a]

AE, n (%)	Continued n = 18: Core n = 18	Continued n = 18: Extension n = 18
Headache	10 (55.6)	7 (38.9)
Insomnia	5 (27.8)	5 (27.8)
Fatigue	4 (22.2)	5 (27.8)
Nasopharyngitis	1 (5.6)	5 (27.8)
Dizziness	3 (16.7)	3 (16.7)
Gastroenteritis	2 (11.1)	3 (16.7)
Pyrexia	2 (11.1)	3 (16.7)
Hypertriglyceridemia	1 (5.6)	3 (16.7)
Nausea	6 (33.3)	2 (11.1)
Influenza	4 (22.2)	2 (11.1)
Arthralgia	4 (22.2)	2 (11.1)
Cough	3 (16.7)	2 (11.1)
Vomiting	4 (22.2)	1 (5.6)
Diarrhea	4 (22.2)	1 (5.6)
Dysmenorrhea	4 (22.2)	1 (5.6)
Hot flush	5 (27.8)	0 (0.0)
Chest discomfort	3 (16.7)	0 (0.0)

AEs coded using MedDRA, version 21.0
[a]AEs occurring in > 15% of the 18 continuing patients in either the core or extension periods

CONCLUSIONS

- **Mitapivat is a novel, first-in-class, PKR activator in clinical testing as a potential disease-altering therapy for patients with PK deficiency**
- **Patients who responded to mitapivat had long-term durable responses:**
  - **Improvements in hemoglobin and other hemolysis markers were sustained at optimized individual doses during the extension period**
- **Chronic daily dosing with mitapivat for a median of 3 years and up to 42 months was well tolerated:**
  - **Consistent safety profile over the duration of treatment**
  - **No new safety signals observed**
- **Two phase 3 trials are underway to further study the effect of mitapivat in patients with PK deficiency**

ACTIVATE N=76
A PHASE 3 CLINICAL TRIAL INVESTIGATING A NOVEL ENZYME ACTIVATOR'S TREATMENT EFFECT IN PATIENTS WITH PK DEFICIENCY

ACTIVATE-T N=20–40
A PHASE 3 CLINICAL TRIAL INVESTIGATING A NOVEL ENZYME ACTIVATOR'S TREATMENT EFFECT IN PK DEFICIENCY PATIENTS WITH HIGH TRANSFUSION BURDEN

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